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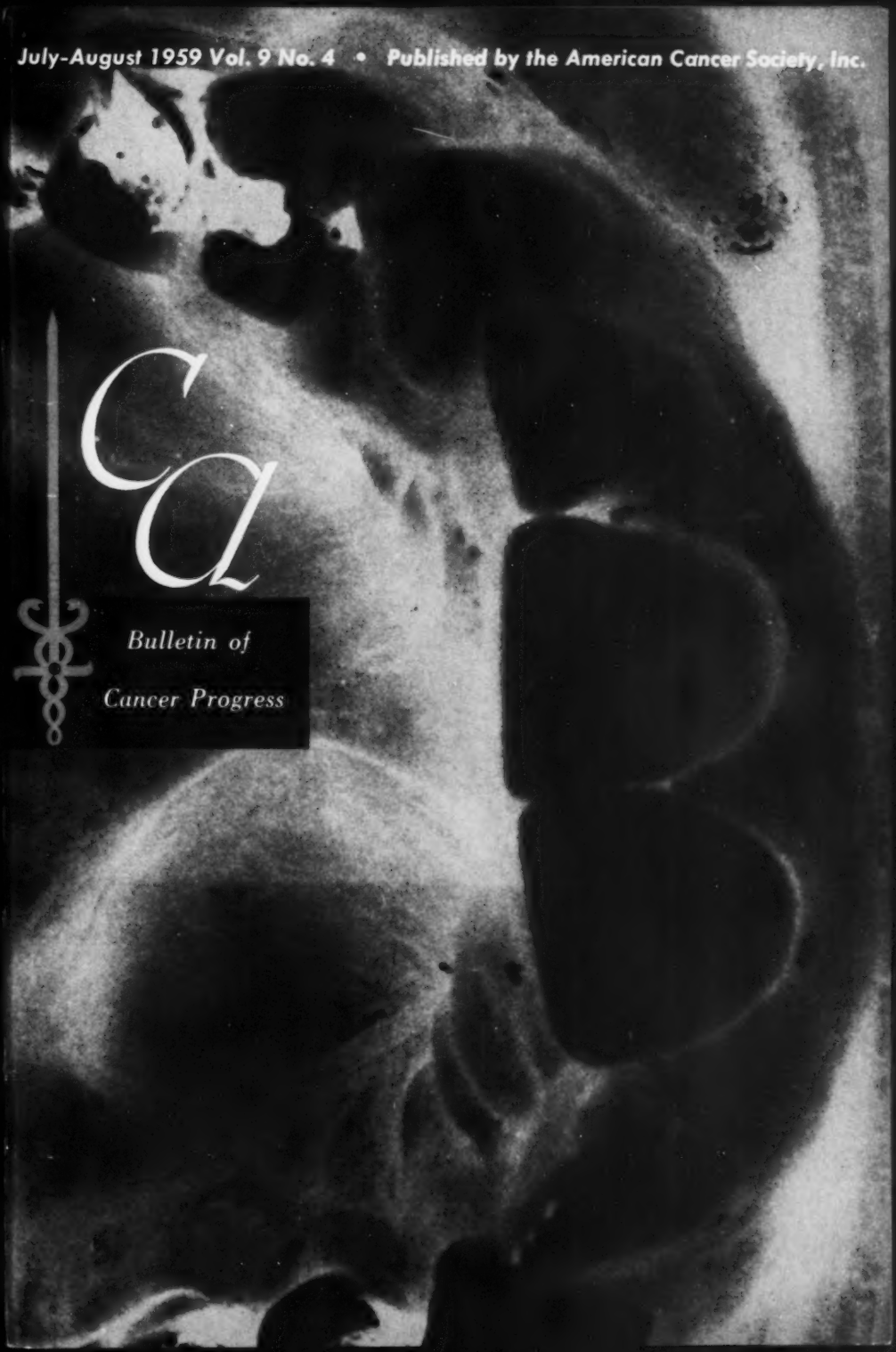


CA

Bulletin of

Cancer Progress

the dental profession has "come of age"

The control of cancer is a cooperative project among physicians, dentists, nurses, other scientists and intelligent and interested laymen.

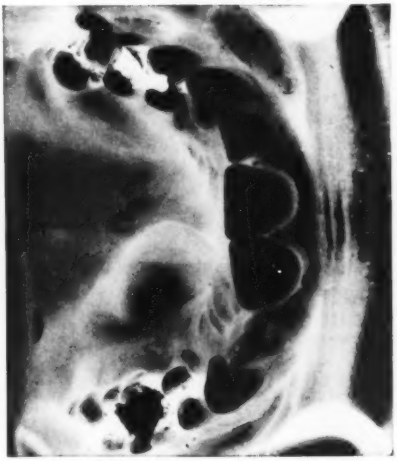
Government, voluntary and private health agencies in recent years have been appropriating large sums for cancer education of the professional groups and the laity. The National Cancer Institute and the American Cancer Society are sponsoring cancer educational projects in medical and dental schools. Today the dental student is instructed in the diagnosis, management and rehabilitation of the oral cancer patient, and is alerted to suspect that any oral lesion that does not heal in two to three weeks of routine therapy may be malignant.

It is particularly appropriate that this issue of *CA* should feature oral cancer since September is the month for the Centennial Session of the American Dental Association and for the meeting of the Federation Dentaire Internationale.

Assembled in this issue are the most modern ideas concerning the role of the dentist in the control of oral cancer. Specialists in oral diagnosis, oral cytology, oral biopsy, orofacial rehabilitation and experimental oral carcinogenesis present their subjects from the standpoint of the dental and medical practitioner.

The American dental profession, now in its hundredth year of organization, has accepted its oncologic responsibilities alongside the medical profession—it has *"come of age."*

Paul E. Boyle D.M.D.



In the control of cancer the dentist's responsibility in the early recognition of oral cancer is as great as the physician's role in recognizing suspected malignant tumors in other parts of the body.

Cover design by Fred Rothberg, New York City.

NEWSLETTER

JULY-AUGUST, 1959

Lung Cancer and Previously Diseased Lungs:

The results of the study by Finke (Rochester, New York) indicate that lung cancer in many, if not most, cases arises in a previously diseased organ. The more prevalent view is that lung cancer usually develops in a previously healthy organ, and if a nonmalignant pathologic state such as bronchitis, tuberculosis, asthma or pneumonia is present, it is due to the new growth or is merely coincidental. In this study, the case histories of 86 patients with lung cancer were reinvestigated thoroughly with regard to previous chronic acute pulmonary disease. In addition, roentgenologic histories of 63 of these patients were obtained. Sixty-five per cent of this group proved to have had long-standing chronic bronchitis, often associated with chronic asthma or suspected of being tuberculosis. In six patients chronic pulmonary tuberculosis had been known to exist ten or more years before the discovery of the cancer. One had silicosis, and two had chronic chest ailments caused by war gas poisoning. In a group of matched patients free of malignant disease, the frequency of chronic pulmonary disease of some type was about half that in the cancer group. It is commonly reported that many patients with lung cancer have had chronic cough long before the supposed onset of malignant growth.

Problems in Tumor Immunity:

Based on present understanding of host-tumor interplay, Hirsch (University of Minnesota Medical School) speculates that tumor cells are constantly being formed in the body by mutation or otherwise, but that those furthest removed genetically from the host tissue are destroyed by the body's immunological defense mechanisms; only those tumor cells most similar to normal cells of the host would thus have a chance to develop into a tumor because the immune response directed against such cells would be very weak. Immunization will work the better, the further removed in type the tumor is from the original host, a condition fa-

cilitated by continued transfer of the tumor from one animal to another. Repeated immunization bolsters the host's immune response. Therefore, it would seem that, in the study of tumor isoimmunity, spontaneous tumors should be used rather than long-transplanted tumors, tissue culture tumors or carcinogen-induced tumors.

Thyroid Cancer After Irradiation:

Rooney and Powell (Emory University School of Medicine) have added ten cases of carcinoma of the thyroid in children 17 years of age or younger to the recorded cases, bringing the total to at least 357. Seven of these ten patients received previous x-ray therapy in infancy or in early childhood for benign conditions. These seven cases can now be added to the reported thyroid cancers in children after irradiation, bringing the total to 121 cases. Approximately one third of all children with thyroid cancer received previous radiation therapy to the head, thorax or neck. Carcinoma of the thyroid in children is being diagnosed more frequently and this correlates with the formerly prevalent use of x-ray therapy for benign conditions in early childhood, suggesting a causative relationship between such x-ray therapy and the subsequent development of thyroid cancer. If this is valid, we should expect, in future years, a decrease in the incidence of this neoplasm in children as the practice of irradiating benign childhood conditions decreases or ceases.

Congenital Virilizing Adrenal Hyperplasia:

Schneeberg and others (Albert Einstein Medical Center, Philadelphia) have reported a rare event -- the occurrence of congenital virilizing adrenal hyperplasia in identical twins. This lends support to the concept of a genetic orgin of this disorder. The incidence of virilizing adrenal hyperplasia has been estimated as one per 67,000 births. Twinning appears once in 85 births and approximately 25 per cent of these are identical; i.e., the rate for identical twins is one in 340 births. Therefore, one would expect the incidence of congenital virilizing adrenal hyperplasia in identical twins to be one per 23,000,000 births.

(Continued after Page 144)

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TOPIC: ORAL CANCER

AT A GLANCE

TREATMENT OF PRECANCEROUS CONDITIONS OF THE ORAL MUCOUS MEMBRANES
by George S. Sharp, M.D.

OROFACIAL REHABILITATION
by Conrad J. Spilka, D.D.S., Donald F. Cole, D.D.S., and T. S. Malson, D.D.S.

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by Sol Silverman, Jr., D.D.S.

DIAGNOSIS OF ORAL CANCER INCLUDING INDICATIONS AND PROCEDURES FOR BIOPSY
by Donald A. Kerr, D.D.S., and James R. Hayward, D.D.S.

NEW DEVELOPMENTS

ARTICLES IN *CA* ARE INDEXED IN CURRENT LIST OF MEDICAL LITERATURE AND QUARTERLY CUMULATIVE INDEX MEDICUS, AND SOME ARE ABSTRACTED IN CHEMICAL ABSTRACTS, BIOLOGICAL ABSTRACTS, EXCERPTA MEDICA AND ABSTRACTS OF WORLD MEDICINE.

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a glance . . .

Precancers of the Mouth

Leukoplakia, papilloma, fissure and ulceration about the mouth are precancerous lesions—lesions which, in inherently susceptible individuals, have a tendency to undergo malignant neoplastic change when subjected to sufficient irritation over a long period. Buccal and lingual cancer may be associated with one or more forms of irritation such as syphilis, tobacco or pathologic dental structures. Syphilitic leukoplakia usually becomes cancer. Syphilitic warts, fissures, gumma and atrophic glossitis may also precede cancer. Excessive use of tobacco produces smoker's tongue and throat with hyperemia, edema and lymphocytic infiltration of the submucosa and erosion and downward growth of the epithelium. Ragged or irregular teeth produce superficial erosions, thickening of the regenerating epithelial layer, lymphocytic infiltration and heterotopia, followed by downward growth of atypical cells. Some benign tumors, originating in inflammatory processes, may be transformed into malignant neoplasms. Transformation of polyps of the tongue into carcinoma has been observed. Regenerative hypertrophy may be a predominant underlying influence in the development of some forms of cancer. Plummer-Vinson syndrome—anemia, achlorhydria and atrophy of the mucous membranes of the mouth and pharynx—is a true precancerous condition. Administration of vitamins A and B with iron constitutes the only satisfactory treatment. Leukoplakia is a chronic, painless inflammation commonly seen in the oral cavity and larynx, and may be found on the dorsum of the tongue, lip, gingiva, buccal mucosa and palate. Etiologic and predisposing factors include syphilis, atrophic glossitis, vitamin A deficiency, alcohol and tobacco, irritation from traumatic occlusion of malposed or carious teeth, improperly fitting dentures and irritation from dental appliances, as crowns and bridges. Electric currents from fillings of dissimilar metals have also been incriminated. "Smoker's patch" is the lay term for oral leukoplakia. About 50 per cent of lung cancer develops upon preexisting leukoplakia. Many cases of leukoplakia can be corrected by simple withdrawal of the known causal factor. Papillomas may occur in any part of the mouth and are precancerous lesions. Their treatment is usually surgical removal. Fibromas are slowly growing tumors, more or less encapsulated and are often the terminal stage of a chronic, inflammatory hyperplasia. Treatment is complete surgical extirpation. Recurrence is the result of incomplete removal. Mixed tumors and carcinomas are the most important tumors of the soft palate. The most frequent mixed tumors of the hard palate are those of the mucous and minor salivary glands.

Lederer, F. L., and Sholnik, E. M.: Precancerous Lesions of the Oral Cavity. In *Pack, G. T. and Ariel, I. M., Eds.: Treatment of Cancer and Allied Diseases, 2nd ed. New York. Paul B. Hoeber, Inc. 1959. Vol. III; pp. 45-52.*

Oral Cancer and the Dentist

The dentist, as custodian of the oral cavity, has the primary duty of a diagnostician. His training in oral pathology places him in a position to recognize oral disease early because he usually sees his patient at frequent intervals. In the control of cancer the dentist has responsibility in the early recognition of oral cancer equal to that of the physician in recognizing early or suspected malignant neoplasms in other parts of the body. Patients depend on the family dentist for guidance in oral health and dentists are accepting this responsibility as a part of their professional service. Complete examination of the oral cavity includes careful inspection of the entire mouth and its contents, pharynx, maxillary antrums and the depending lymphatics. Procrastination regarding a questionable lesion, a wrong diagnosis or a failure to recognize the existence of an abnormality may cost the life of a patient who has placed confidence in the opinion of his dentist. It is a grave obligation that the dentist faces.

Cameron, J. R.: New horizons in dentistry. J. Am. Dent. A. 57:693-698, Nov., 1958.

Oral Cancer

Cancers of the oral cavity and face are accessible to sight and touch and should, therefore, be detectable early if proper examination is made. Among the causative factors of these cancers are sunlight and smoking. Cancers of these sites spread by direct invasion through lymphatics as a rule and only rarely by the blood stream to distant sites. Because of their accessibility these cancers can often be cured by surgery or radiation in their primary sites and even when in advanced stages they can be cured by modern methods such as surgical dissection in continuity. Oral cancers include those of the lips, buccal mucosa, gums, palate, tonsils, floor of the mouth and tongue. The five-year cure rate of cancer of the lip is approximately 75 per cent; of the tongue, floor of the mouth and cheek, about 30 per cent; of the palate, about 35 per cent and of gums and tonsils, about 20 per cent. The dentist shares a great part of the responsibility for recognition of mouth cancer since about half of these patients consult a dentist first. All chronic ulcerative or nonhealing lesions in the mouth should be considered to be cancer until proved otherwise. Biopsy should be done without delay and, if cancer is demonstrated, treatment should follow immediately to avoid any potential spread. About 40 per cent of all oral cancers have metastized to the neck nodes at the time of diagnosis. Prevention of oral cancer includes elimination of the causative agents such as excessive sunlight, smoking, bad mouth and teeth hygiene, infections and mechanical and chemical irritants. The development of oral cancer on leukoplakia makes recognition, observation and treatment of such thick, white patches on mucous membrane important. Papillomas of the mouth should be removed as they may possibly undergo malignant change. Tumors of the parotid gland should be removed early. "Ripening" is to be condemned. Tumors of the submaxillary gland have a very high tendency toward malignant change and spread and must be carefully differentiated from inflammation. In view of a precise body of knowledge concerning the causation, development and spread of cancer in the head and neck region, these cancers can be readily observed and frequently can be cured.

Sage, H. H.: Oral and facial cancer. New York J. Med. 59:1113-1116, March 15, 1959.

Cancer of the Head and Neck

Oral cancer accounts for more than 5 per cent of all human cancers. Long-time exposure to sunshine, wind and frost is by far the most frequent predisposing factor in carcinoma of the lower lip. Carcinoma of the lip is very rare in Negroes. Cancer of the buccal mucosa has a higher incidence among smokers than among the general population and is still more common in individuals who habitually chew tobacco. Poor oral hygiene, malnutrition, trauma and other forms of localized irritation are important etiologic factors. Hy-

pertrophy of the mucous membrane due to repeated trauma such as biting or malfitting dentures must be differentiated from true tumors. The high incidence of cancer of the oral cavity, pharynx and esophagus in Swedish women is due to iron deficiency, Plummer-Vinson syndrome. Leukoplakia and hyperkeratosis are considered to be premalignant lesions. Leukoplakia is hypertrophy of the squamous epithelium which appears microscopically similar to the hyperkeratosis seen in the skin. It differs from skin hyperkeratosis in that the surface of the mucous membrane is constantly moistened and does not peel off as readily. Therapy of leukoplakia should begin by removing all forms of irritation—ill-fitting dentures, bad teeth, excessive smoking and hot and spicy foods. If the leukoplakia persists electrodesiccation, cautery or surgery is indicated. The most important procedures in diagnosis of carcinoma of the oral cavity are inspection and palpation. Since all these cancers are either visible or palpable, any suspicious lesion of the mouth should be considered cancer until biopsy rules this out. Repeated biopsies may be necessary. In the United States, cancer of the lower lip is the most common form of oral cancer. The second most common form is cancer of the tongue. Cancer of the buccal mucosa is one third to one quarter as common as cancer of the tongue. Cancer of the lower gingiva accounts for about 5 per cent of oral cancers. Cancer of the palate is rare in this country. The most important point in determining prognosis of oral cancer is early diagnosis. Surgery, radiation and their combination are the methods of curative treatment. Medical treatment consists of relief of pain, maintenance of nutrition, prevention and treatment of respiratory and vascular complications. Chemotherapy for metastatic or inoperable head and neck cancer is generally disappointing. Chemosurgery may be of value in some inoperable cases. Estrogens have been used in advanced salivary gland tumors with some success.

Kofman, S.: Cancer of the head and neck. Ann. Int. Med. 48:731-746, April, 1958.

Oral Melanoma

Primary malignant melanoma of the oral cavity is a rare tumor but not so rare that it should be forgotten. It occurs more often in men than in women. Nearly 75 per cent of the patients are more than 40 years of age, the average age of this group being 50.5 years. The most common site of involvement is the superior maxilla. The hard palate, the alveolar mucosa and the soft palate, in that order of frequency were involved most commonly. In nearly 30 per cent of the cases there was oral pigmentation at the site at which the neoplasm originated and this pigmentation had appeared from a few months to several years before the tumor. The disease occurs in all races. Lymph node metastases occurred in approximately half the cases. In approximately one fifth of the cases there was roentgenographic evidence of generalized metastases. Of 61 patients followed, 51 died of the disease. In 24 patients the survival period averaged 18.5 months after diagnosis. Only three patients lived more than five years. In view of the serious prognosis of the disease early recognition of the lesion and institution of radical surgery is desirable. The appearance of melanin pigmentation in the mouth and its increase in size and in depth of color should be viewed seriously.

Chaudhry, A. P.; Hampel, A., and Gorlin, R. J.: Primary malignant melanoma of the oral cavity; review of 105 cases. Cancer 11:923-928, Sept.-Oct., 1958.

Oral Cancer

During the past 15 years better anesthetics, intratracheal anesthesia and blood banks have made possible tedious operations with little shock and of six to eight hours duration. Antibiotics have eliminated the dread of infections and pneumonia following extensive operations when both mouth and neck are in the same operative field, and more frequent use of tracheotomy has lessened sudden operative deaths from aspiration of blood and mucous. Improvements in plastic and reconstructive surgery and the use of

newer and more efficient prostheses have contributed to earlier and better rehabilitation of patients with their return to active, happy, social and economic lives. Chronic trauma is an important etiologic factor in cancer of the mouth. Ill-fitting dentures, ragged, unkempt teeth and deficient oral hygiene are contributory factors. Tobacco and alcohol are added irritants and play an important etiologic role in cancer of the mouth, oropharynx and hypopharynx. The first symptom of cancer of the lip is usually a small scaly area, a wart or a fissure that fails to heal under local treatment. Slight induration under any of these benign lesions is suggestive of invasion and neoplasm. In the parotid area, the most common first sign is a painless lump. Pain in a parotid tumor is very suggestive of cancer. Tumors of the submaxillary gland are usually painless. Clinical diagnosis of cancer of the lips or oral cavity is usually made on inspection and palpation. No diagnosis of cancer in these areas should be made without biopsy. Two or more biopsies may be necessary since chronic inflammation in the mouth often overshadows cancer. Biopsy tissue should be taken from the border of the lesion so that normal and abnormal tissue can be compared. Most of the common complications of conventional voltage therapy are reduced with the proper use of supervoltage therapy. In the earlier use of supervoltage therapy ten years ago there were serious complications such as severe fibrosis and even necrosis sometimes affecting the jaw and the temporal maxilla. This necrosis was largely bone devitalization with superimposed infection.

Ward, G. E. (Moderator); Chambers, R. G. (Substitute Moderator); Copeland, M. M., and Bloedorn, F. G., (Panel Members): Carcinoma of the head and neck; symposium. Maryland M. J. 7:340-357, July, 1958.

Cancer of the Floor of the Mouth

Twenty patients with cancer of the floor of the mouth were followed for more than three years and 11 for more than five years after surgical removal of cancers of the floor of the mouth. The absolute survival rates are 7 of the 11 patients at the end of five years and 15 of the 20 patients at the end of three years. Results of therapy must be evaluated in terms of disability produced as well as absolute survival figures. Surgery produces a noticeable speech defect but speech is not interfered with significantly unless it has been necessary to excise a large portion of the tongue because of deep invasion of tongue musculature. Diminished mobility of the tongue interferes with handling of certain foods sometimes making it necessary for the patient to eat mostly soft foods and liquids. Disabling as are these complications they are less so than the necrosis and ulceration so frequently following heavy irradiation. Almost universally appearing in histories of this series of patients was heavy cigarette smoking and concomitant ingestion of alcohol. These points of personal history were so prominent as to lead the authors to advise all of their patients with cancers of the mouth to discontinue these habits, especially smoking. None of the patients was a nonsmoker who drank large amounts of alcohol, but a few were heavy smokers who drank no alcohol. The great majority both smoked and drank heavily.

Alford, T. C., and Klopp, C. T.: The surgical treatment of cancer of the floor of the mouth. Cancer 11:1-3, Jan.-Feb., 1958.

Cancer of Salivary Glands

In the parotid and other salivary glands a considerable proportion of the tumors are of very doubtful malignancy, making distinction between benign and malignant more difficult than in other sites. Some tumors of the salivary glands infiltrate neighboring structures without giving rise to distant metastases, and others metastasize without showing any macroscopic or histologic features indicative of malignancy. The general term, salivary glands, includes not only the parotid, submaxillary and sublingual glands, but also the minor salivary glands in the mucosa of the palate, lips, cheeks and tongue. Primary tumors of the salivary gland constitute approximately 1 per cent of all malignant tumors. Since about one quarter or one

third of these tumors are malignant, about 0.3 per cent of all cancers are malignant tumors of the salivary glands. For every 100 tumors of the parotid there are approximately ten of the submaxillary, ten of the minor salivary glands and one of the sublingual gland. It is probable that the incidence of salivary gland tumors varies in different races. Tumors of the salivary glands, benign and malignant, occur at all ages. These tumors spread by lymphatic and blood stream dissemination. About three quarters of all parotid tumors are of the mixed type. Only about half of those of the submaxillary and minor salivary glands are of this type. Fear of injury to the facial nerve has made an inadequate shelling out of parotid tumors the standard treatment. As a result recurrence rates are high, not because the tumors are multicentric but because of incomplete removal. About 3 per cent of mixed parotid tumors become malignant. Mucoepidermoid tumors of the salivary glands extend by local infiltration and metastasize to regional lymph nodes in about half, and to distant viscera in about a third, of all cases. It is as difficult to distinguish between benign and malignant tumors of the minor salivary glands as of the major glands. Tumors occur in the minor salivary glands about as often as in the submaxillary glands. The majority arise in the palate and are of the mixed type without evidence of cancer. Over half of them recur after simple enucleation. With wider excision recurrence has not been noted. Benign connective tissue tumors, hemangiomas, lipomas and neurinomas occur in the parotid gland. Sarcomas are exceedingly rare and must be differentiated from spindle cell and round cell carcinoma.

Thackray, A. C.: Malignant tumours of the salivary glands. In *Raven, R. W., Ed.: Cancer, vol. 2. London. Butterworth & Co., Ltd. 1958; pp. 154-167.*

Oral and Laryngeal Cancer

A majority of cases of cancers of the mouth and larynx are avoidable. In a series studied at Memorial Hospital, New York, the claim that irradiation of teeth is an etiologic factor in cancer of the mouth can not be confirmed. Tobacco chewing, smoking and heavy alcohol consumption were found to be etiologically important. Preventive measures are moderation in smoking habits first of all and in consumption of alcoholic beverages. In Sweden cancers of the oral cavity are more common in women than in men due to the prevalence of Plummer-Vinson's disease. In India the disease is closely correlated with betel nut chewing and the smoking of bidis, small cigarettes. Smoking causes more cancer of the lung than of the oral cavity perhaps because the oral cavity has a more immune type of tissue than the lung epithelium. In this country cancer of the mouth is more common in men than women because men smoke and drink more. With the knowledge available at present cancer of the oral cavity, larynx and lungs may be considered to be preventable.

Wynder, E. L.: Environmental factors in oral and laryngeal carcinogenesis. Symposium on Cancer of the Head and Neck. New York, American Cancer Society, Inc. 1957.

Cancer of Lip, Tongue, Mouth and Jaw

Approximately 2 per cent of all cancers in males are of the lip; 0.1 per cent in females. Incidence of cancer of the buccal cavity in man has been declining in recent years but not of cancer of the lip. About 4 per cent of mixed salivary tumors occur in the lips. Sarcoma of the lip is rare. Carcinoma of the lip is very common in India—probably the result of the habit of placing powdered tobacco inside the lower lip. About one third of cases of carcinoma of the upper and lower lip are preceded by leukoplakia, a bleb or an ulcer. Cancer of the lip is most common among pipe smokers and farmers. Sunlight is a probable contributing predisposing factor. Early carcinoma of the lip is almost indistinguishable from leukoplakia. About half the cases have ulcerated when diagnosed. More than 90 per cent are of the lower lip in men. In women one tumor in four is on the upper lip. Carcinoma of the lip, enlarging locally, spreads directly to the adjacent gum and jaw.

Spread to lymph nodes occurs relatively late in comparison with carcinoma of the tongue. At the time of diagnosis about 35 per cent of cases have lymph node involvement. Clinical manifestations of blood-borne metastases are rare; but, since autopsies are seldom performed on account of the obvious diagnosis of these cases, general dissemination is probably less rare than is generally supposed. Approximately 3.5 per cent of all cancers in men and 0.5 per cent in women are of the tongue. In India cancer of the mouth, including the tongue, is more common than in Europe and North America. There is no difference in the incidence of cancer of the tongue between South African Europeans and native Bantus. Leukoplakia is an important precancerous condition of the tongue; but, unlike that of the lips, it is often associated with tertiary syphilis. A positive Wassermann reaction may be expected in one third of cases of carcinoma of the anterior two thirds of the tongue. Leukoplakia and syphilis are less commonly in association with carcinoma of the posterior third of the tongue. Agricultural occupation, smoking and chewing betel nut or mixtures of betel and tobacco are etiologically important. There is an association between carcinoma of the base of the tongue and smoking and chewing tobacco. In squamous carcinoma the anterior parts of the tongue are affected in two thirds of the male cases and in four fifths of the female cases. An ulcer is present in the great majority of cases. In a few the tumor is warty and papillomatous, or an indurated fissure or nodular area is present. Some wrinkling and cracking of the surface is usual. The lesion is usually lateral. Cancer of the tongue is more likely to invade lymph nodes than are histologically similar tumors of the lips and buccal mucosa. Approximately half the cancers of the anterior two thirds and three quarters of those of the posterior third metastasize to the cervical lymph nodes. By direct extension, cancer of the tongue spreads to the floor of the mouth, fauces, epiglottis, gums and jaws. Necrosis and sepsis in the mouth commonly produce fatal bronchopneumonia. Metastatic lesions in the cervical nodes may ulcerate through the skin or invade the thyroid gland and jugular veins with resultant hemorrhage and blood-borne spread. The incidence of oral cancers in men is approximately 4 per cent of all cancers, and in women approximately 0.5 per cent. In order of frequency intra-oral cancer affects the floor, alveolar mucosa, palate and mucosa of the cheek. Secondary carcinoma of the mouth may occur rarely—even from a primary testicular tumor. Leukoplakia of the mouth is precancerous but precedes buccal cancer less commonly than in the tongue. General, dock and agricultural laborers are unusually liable to buccal carcinoma. Pipe smoking in London and cigar smoking in India are statistically associated with leukoplakia and cancer of the hard palate. The Indian cigar is smoked with the lighted end inside the mouth. Betel nut chewing, especially when tobacco is mixed with the quid, leads to leukoplakia and cancer of the buccal mucosa. Squamous carcinoma is usually a localized swelling or nodular thickening that may become quite large and polypoid. Ulceration is often present when trauma is a factor. Most malignant melanomas are in the hard or soft palate or upper alveolus. Squamous carcinomas of the mouth extend to alveolar bone, and carcinoma of the upper alveolus or palate may invade the maxillary antrum. Lymphatic spread to the cervical lymph nodes is less early than in cancer of the tongue. The jaws contain dental structures that make them liable to special tumors as well as to malignant tumors of bone. Dental tumors may be benign or highly malignant squamous carcinomas. An intermediate type is the ameloblastoma (adamantinoma). About 3 per cent of all sarcomas occur in the jaw. Microscopic appearances of true sarcomas of the jaw are the same as bone sarcomas elsewhere. In adults any carcinoma producing bone metastases occasionally involves the jaws. Metastases have been reported from thyroid, prostate, breast, kidney, lung and stomach.

Cruickshank, A. H.: Malignant tumours of the lips, tongue, mouth and jaws. In *Raven, R. W., Ed.: Cancer, vol. 2. London. Butterworth & Co., Ltd. 1958; pp. 58-74.*

Mouth Cancer and the Dentist

Members of the dental profession hold a position of unique advantage with regard to the early diagnosis of cancer of the oral cavity and the prophylaxis against this disease. Malignant tumors of the mouth occur commonly in persons who otherwise apparently enjoy perfect health. Many of them have seldom, if ever, needed to consult a physician, at least not for any complaint that would require a thorough examination of the oral cavity. The medical profession is powerless to provide early diagnosis and prophylaxis for this group of people. On the other hand, since it is becoming an increasingly widespread practice, from childhood on, to have a thorough dental examination once or twice a year, *the dentist can examine the oral cavity periodically under the most desirable conditions.* If the dentist does not avail himself of this unusual opportunity for the early recognition of cancer, the irreparable loss to the public health is obviously great. By training and practice, the dentist is familiar with the normal anatomy of the oral cavity and hence should be able to recognize any departure from the normal. He has but to realize that his responsibilities do not end with the care and treatment of the teeth and their appendages alone; and that in every case in which he is able to discover a malignant tumor, it is possible that he has been instrumental in saving a human life. The symptoms of early mouth cancer are seldom distressing or markedly painful. When a malignant tumor first appears in the gum, the hard palate, the edge of the tongue, or the cheek, the location of the lesion and the mild character of the symptoms logically suggest to the patient that there may be some trouble with the teeth. In such cases, therefore, it is natural for the patient to consult his dentist first.

Martin, H.: Mouth Cancer and the Dentist; a Monograph for the Practicing Dentist. New York. American Cancer Society, Inc. 1949; pp. 8-9.

Dental Centennial

Charles C. Darlington, M.D., F.C.A.P.

The American Dental Association will celebrate the 100th anniversary of its founding, in New York City September 14-18. In addition, the Federation Dentaire Internationale will hold its 47th annual meeting September 12-19. Meetings will be at the New York Coliseum.

The object of the Association is "to encourage the improvement of the health of the public and to promote the art and science of dentistry." These objectives are carried out through education, research, practice and public and professional relations. Increasing attention is being given to the role of the dentist in early recognition and diagnosis of cancer of the head and neck, and of the mouth and its associated parts.

The centennial meeting will open with a congratulatory message from President Eisenhower, greetings from Mayor Wagner and the official call from Dr. Percy T. Phillips, President of the American Dental Association. Plans include administrative committee meetings, scientific symposia, discussion groups, essays, table clinics, lectures, motion pictures, exhibits and closed circuit black and white and color television presentations. There will be tours, social events and entertainment.

Both the New York University Dental Center with its new expansion and modernized facilities, and Columbia University School of Dental and Oral Surgery will act as host schools for this celebration.

An unusual contribution epitomizing the progress made by dentistry in the past century is shown in the centennial issue of the *New York Journal of Dentistry* of May 1959.

Professor of Pathology and Director of Cancer Teaching, New York University College of Dentistry, New York, N. Y.

Treatment of Precancerous Conditions of the Oral Mucous Membranes

George S. Sharp, M.D.

In cancer control, prophylaxis has been one of the least investigated among the various therapeutic measures tried. However, in oral cancer, definite studies are showing that precancerous conditions can be returned to normal. Results indicate that certain substances and combinations (hitherto unknown) transform precancerous and other abnormal mucous membranes into healthy tissue.

A study was made of a series of 350 patients, all with subjective complaints referable to the oral mucous membranes. In order to initiate this study and make it as objective as possible, only patients who were unable to tolerate their dentures full time were selected to test the therapeutic effectiveness of various medications. Ten per cent, or 34 patients, were acceptable. Their symptoms were described as soreness, rawness, burning and dryness, primarily of the membranes in contact with the dentures. Removal of the dentures gave immediate partial relief from discomfort, but all of the patients were unable to tolerate their dentures during the night.

Atrophic and degenerative changes in the oral mucous membranes were observed in all of these patients. In addition, other precancerous states such as leukoplakia, extensive superficial scarring, fibroepithelial hyperplasia, erosions and even superficial ulcerations were frequently noted.

General as well as local conditions must be considered in the treatment of the sore mouth. Obviously, dentures must be properly adapted, and allergy or sensitivity to denture material must be excluded. With these factors ruled out, the problem becomes generalized and an underlying metabolic deficiency is indicated. This might include abnormal liver function, abnormal assimilation, basic metabolic defect of some type or deficient intake.

The relationship between atrophy of the oral mucous membranes and the state of the mucosa throughout the body has been reported. Many different therapeutic preparations have been recommended. Over a period of years we have tried vitamin supplementation in many combinations, the marketed protein supplements, yeast and crude liver. Yeast and liver products partially relieved the symptoms, but were poorly tolerated because of digestive distress and unpalatability. Finally a tablet was prepared* containing whole desiccated liver, 750 mg., vitamin B_{12}, 5 mcg., riboflavin, 1.5 mg. and folic acid, 0.5 mg. The dose prescribed was 3 to 6 tablets daily, in addition to dietary instruction.

The primary study was made with 34 selected patients with low tolerance to dentures syndrome, observed under treatment as outlined above for six months. At the start of treatment, none of these patients was able to tolerate dentures full time. Within two to six weeks from the commencement of treatment, 30 of the patients were able to wear their dentures for 24 hours in comfort. Six patients continued to have intermittent mouth soreness or dryness of the oral surfaces other than the gingivae. The remaining 24 were completely relieved of all oral complaints.

Summary

Patients with typical precancerous lesions of the oral mucous membranes have shown consistent objective and subjective improvement on a simple supplemented dietary regimen which appears to open possibilities in the prevention of oral cancer.

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Abstract of paper read before the James Ewing Society, New York City, April 2, 1959.

*Mucoplex (Stuart Pharmaceutical Company, Pasadena, California).

Orofacial Rehabilitation

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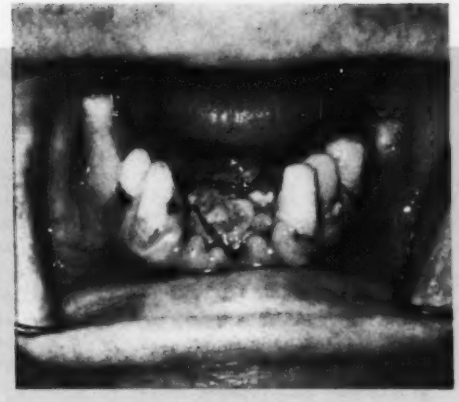

Fig. 1. Squamous cell carcinoma of floor of mouth of two years' duration.

The diagnosis, treatment and rehabilitation of patients with extensive oral and facial lesions has become a formidable and complicated problem. No one clinician or specialist is able adequately and satisfactorily to meet all of the problems which arise. In order to handle these cases successfully, there must be a concerted and conscientious effort of a carefully selected group acting in perfect accord. This group functioning harmoniously as a coordinated team should include all of the medical and dental specialists with adequate training in this type of surgery and rehabilitation.

The oral surgeon, the prosthodontist and the general practitioner of dentistry, each, because of his training and experience should become an integral part of this team. Each should be consulted routinely *prior* to radical surgery in order that replacement of the lost oral structures can be planned accurately, and the oral cavity be made to simulate the normal.

The prosthetic restoration of missing parts of the jaws and face is indicated where surgical procedures cannot be expected to produce satisfactory functional or cosmetic results.

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When a section of the palate or alveolar ridge is destroyed, a prosthesis may be preferable to surgery as a means of restoration. The prosthesis may also be used as a temporary measure prior to, or during surgical treatment, in order to maintain the position of the tissues as healing progresses. Use of such appliances replaces deficient tissue adequately and satisfactorily, hastens healing, prevents contractures and adhesions and restores the contour of the affected parts.

The addition of these dental specialists consolidates the surgical team. This team cooperating as an integrated group is now well equipped to handle all of the various surgical and therapeutic problems encountered in the treatment of oral and facial neoplasms.

In order to appreciate fully the importance of coordinated treatment by surgery and prosthesis, it is necessary for the prosthodontist to have a working knowledge of the problems encountered during surgery in order to construct the appliances accurately. The surgeon also, must become thoroughly acquainted with the possibilities and mechanical principles of these appliances in order to harmonize his surgical technique with the prosthetic procedures.

Fig. 2. Study casts showing position of short posterior fragments.

Fig. 3. Cast cap splints holding fragments in position until further surgery.

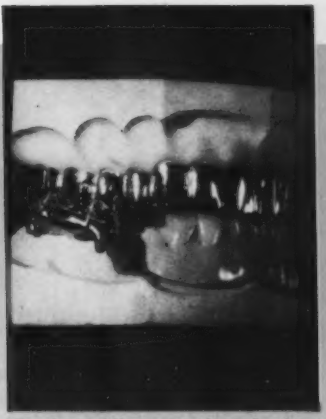

Fig. 4. Acrylic restoration of missing structures molded over bar to prevent tissue contractions.

In many instances the dental specialist is the "forgotten man" when surgery is being planned for extensive oral and facial lesions. It is not until the postoperative course when reconstruction and rehabilitation are being considered that the aid of the dental specialist is solicited. This is always unfortunate in that the patient fails to receive the best possible treatment, not only for the eradication of disease but also for eventual restoration of function and appearance and subsequent return to society.

In those instances where the dental specialist is part of the cancer team, this situation does not exist since he is given an opportunity to voice his opinion during the planning stage and at the appropriate time in the course of diagnosis, treatment and rehabilitation.

It is this group approach which yields the best treatment for the patient with a minimal loss of time. Prevention of disfigurement is attained by a proper and accurate prosthesis inserted at the optimal time.

In extensive lesions of the floor of the mouth involving the mandible (Fig. 1), where radical surgery is contemplated, the control of the remaining mandibular fragments will depend upon the state of the remaining structures.

The problem becomes difficult because of the mobility of the two short posterior fragments (Fig. 2). When both remaining fragments contain at least one tooth bilaterally, the problem is easily solved by the use of cast cap splints with screw-connecting bars. These splints hold the fragments in excellent position until more definite surgery is planned (Fig. 3). It also prevents the fragments from being displaced medially by the contraction of the fibrous tissue. Missing structures can be replaced by an acrylic restoration which is molded over the bar with sufficient bulk to prevent tissue contraction. At a later stage this acts as a supporting aid during the reconstruction of the soft tissues (Fig. 4).

Extensive tumors (Fig. 5) of the maxilla frequently cause gross deformities which may present a large osteolytic defect in the hard palate with erosion into the nasal fossa. The surgical excision of these tumors results in a large perforation of the hard palate with a permanent opening into the nasal fossa and maxillary sinus (Fig. 6).

In situations such as this, the application of an obturator may completely overcome the functional disability (Fig. 7). The prosthesis can be used most satis-

Fig. 5. Clear cell carcinoma metastatic from kidney.

Fig. 6. Postoperative defect after surgical removal of tumor.

Fig. 7. Prosthetic device for closure of defect.

Fig. 5

factorily in these cases. Not only does it completely close the defect, replace the lost teeth and permit normal eating and speaking, but it also saves the patient from undergoing an additional operation. Surgery, even though successfully performed, cannot possibly attain the satisfactory results which may be secured with a well-fitting prosthesis.

Unfortunately, some patients with these large defects are sent to the prosthodontist long after the original operation. Under such circumstances, in addition to the defect of the maxilla, contraction of soft tissue may offer an additional obstacle to the successful construction of a prosthesis. It is always preferable to make plans prior to the operation in order that some type of temporary appliance may be inserted within a week after the operation. This greatly lessens contraction of the surrounding soft tissues while the wound is healing, and enhances the patient's comfort and mental attitude by lessening his difficulty in speech and mastication.

Where the tumor involves the anterior part of the hard palate, alveolus and maxillary gingival structures, necessitating partial bilateral resection of the maxilla (Fig. 8), an almost complete upper denture with attached obturator must be constructed (Fig. 9). Sufficient acrylic is needed to add bulk to the appliance to build up the space formerly occupied by the maxilla, and to restore normal contour to the anterior part of the mouth. It is necessary for the appliance to provide adequate fullness to the upper lip as well as to lend improvement to the facial contour (Fig. 10).

A tumor which has been shown by histopathologic examination to be benign (Fig. 11) may, because of its slow growth, enlarge asymptomatically, eroding into the

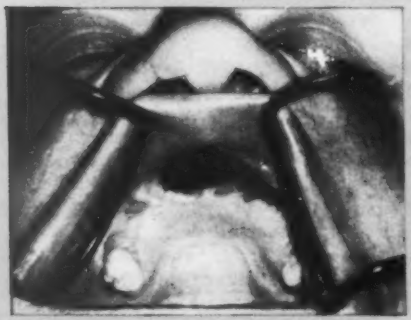

Fig. 8. Postoperative defect after surgical excision of squamous carcinoma.

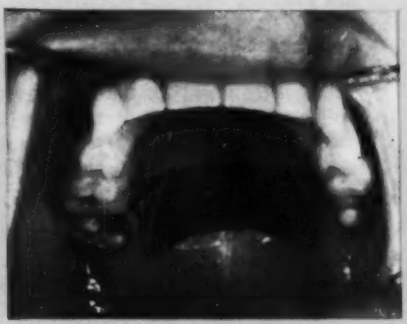

Fig. 9. Construction of upper denture with an attached obturator.

Fig. 6

Fig. 7

maxillary bone and invading the floor of the nasal fossa or maxillary antrum. Excision of this tumor requires extirpation of part of the hard palate and alveolar bone resulting in a large opening into the maxillary antrum and nasal fossa. However, this defect can be closed by use of a modified obturator (Figs. 12 and 13).

In all cases of benign tumors, the maxillary tuberosities should be preserved if at all possible.

An acrylic splint should be made prior to the removal of the tumors, and inserted as soon as the patient is able to tolerate it. This will restore the normal contour of the mouth and permit the patient to eat comfortably and to speak intelligibly.

Repair should be planned immediately after surgery. Reconstruction may be considered within two to three weeks after the removal of the tumor. The mucous membrane will have healed sufficiently in this period to permit an impression of the site. The scar will be soft since contraction has not begun, and the muscles still can be stretched. This second prosthesis may then be worn and adjusted as the defect requires. Often these appliances will function satisfactorily for a considerable length of time before it becomes necessary to reconstruct them.

Summary

The patient who has incurred extensive defects of the oral and facial structures will be benefited most by the services of a rehabilitation team of which each of the participants has a comprehensive knowledge of the others' problems, both surgical and prosthetic.

The surgeon needs to become thoroughly acquainted with the possibilities of modern prostheses, as well as with the time

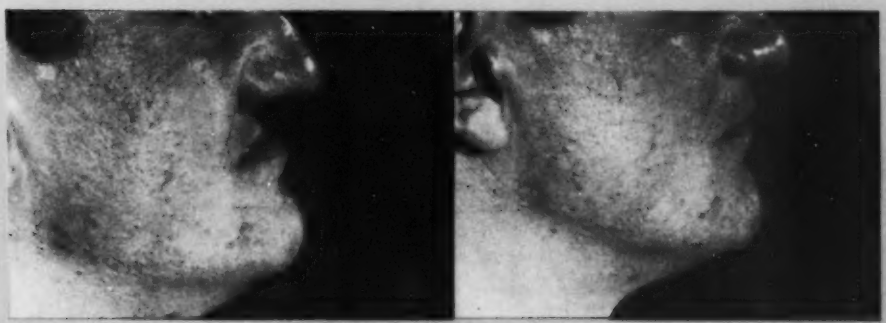

Fig. 10. Although patient suffered extensive functional disability, the prosthesis improved facial contour and restored the ability to eat and speak.

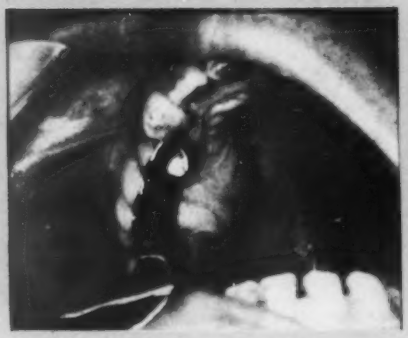

Fig. 11

Fig. 12

Fig. 13

Fig. 11. Ossifying fibroma of several years' duration with invasion of maxillary sinus.

Fig. 12. Modified obturator restoring ability to speak clearly.

Fig. 13. Prosthesis in place, appliance closes defect, replaces teeth, permits intelligible speaking.

for their insertion in order to harmonize the surgical technique with the prosthetic procedure.

The prosthodontist needs to become thoroughly acquainted with the problems of successful surgery.

An objective understanding and acceptance of each other's methods will achieve a cooperative relationship which is desirable if the most satisfactory rehabilitation of these orofacial cripples is to become a reality.

Smoking and Oral Cancer

From statistical studies of the smoking habits of lung and oral cancer victims, and from experimental studies of the effects of tobacco smoke on animals, there appears to be little doubt that smoking increases the probability of dying from cancer as compared with other causes of death. The likelihood that smoking increases the possibility of oral carcinoma cannot be discounted. The present stage of discussion suggests that each individual must decide whether smoking is worth the definite but undetermined risk.

Robinson, H. B. G.: Neoplasms and "precancerous" lesions of the oral region. In *Robinson, H. B. G., Ed.: Tumors of the Oral Regions. Philadelphia. W. B. Saunders Company. 1958.*

Experimental Oral Carcinogenesis

Barnet M. Levy, D.D.S.

In any discussion of malignant growth, a consideration of cancer of the mouth is of importance. In the United States, oral cancer occurs at a rate of about 25 per 100,000 population or in about 23,000 people a year. Moore reported that of the 19,192 patients treated at Memorial Hospital, New York City, over a 12-year period, 20 per cent had malignant disease of the intraoral and neighboring regions. Next to genitourinary cancer, oral cancer was the most common malignant tumor treated at this hospital.

Cancer of the mouth is primarily a disease of men. In 1954, more than 4000 men and fewer than 1200 women died of oral cancer in the United States. In India, cancer of the mouth is the most common form of malignant tumor in men, accounting for about 40 per cent of all cancers diagnosed in Bombay's Tata Memorial Hospital.

These limited statistics suggest the importance of environment, both external (geographic location) and internal (sex), on the incidence and location of malignant growth.

Although cancer research per se is only about 60 years old, the literature is so vast that it would be impossible to write a comprehensive review. Some of the fundamental aspects of experimental carcinogenesis must be elaborated, however, if we are to attempt to understand the problem of oral malignant growth. Cowdry pointed out that the history of cancer research cannot be taken up in an orderly fashion. One reason for this is that many specialists in the fields of biological and physical sciences have attacked the cancer problem, each from within his own special sphere of interest. Great progress has been made by the geneticist, by the pathologist, by the electron microscopist, by the virologist, by the endocrinologist and so on, each adding to a better understanding of the problems of growth in general and of malignant growth in particular. Dentistry, too, has added to the knowledge of malignant growth with special reference to intraoral disease.

Although it is sometimes convenient to consider that experimental carcinogenesis apparently deals with localized small groups of cells, we must constantly remember that no matter how small the group or how well localized the cells under consideration seem to be, they are an integral part of the individual. This concept of individuality, which is one of wholeness or complete integration, is extremely important in the field of oral cancer research. We must recognize that man is a complex biological unit in a complex environment and that individual cells or groups of cells are influenced not only by their external environment, but also by their neighboring cells as well as by their distant relatives. It is best to consider cancer of the mouth as a disease of an individual which is manifested by the local mouth lesion. With this concept in mind, we can review some of the experimental work which has been done which might relate to the problem of intraoral malignant disease.

Superficial examination of oral mucosa and of skin might lead one to believe that they are identical. They are both covered by a layer of squamous epithelial cells. The epidermis covers a corium or a fibrous tissue layer in both the skin and the mouth. If one examines the cells of both areas they are found to be indistinguishable. There are, however, definite differences. The skin has as its appendages such organs as sebaceous glands, hair follicles and sweat glands. The normal mucosa rarely, if ever, has sweat glands or hair follicles, but has as its appendages teeth and mucous glands which the skin does not have.

One of the most important differences between the skin and the oral mucosa is

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the environment in which each exists. The environment of the skin is usually air and is relatively dry. The environment of the oral mucosa is usually saliva and is relatively moist. There are many physiological differences between the external surface of the body and the lining of the internal surfaces of the body, not the least of which is the ability of the mucous membranes to absorb materials from their environment more rapidly than does the skin.

Since there are morphological as well as physiological differences between the epithelium of the skin and the epithelium of the mouth, those interested in the problem of oral carcinogenesis have to answer such questions as: Are the cells of the oral mucosa different from the cells of the epidermis in their reaction to carcinogens, and does the difference in the environment of the cells of the oral mucosa influence the biology of those cells? Much work has been done in the field of experimental carcinogenesis of skin. Of this, the early work on skin carcinogenesis has been reviewed by Shear and by Cowdry. If a polycyclic hydrocarbon, like 20-methylcholanthrene, is dissolved in benzene and painted on the skin of a mouse, malignant epithelial tumors develop at the site of application of the carcinogen. These tumors do not develop immediately. There is a lag period between the time of application and the appearance of the tumor. This time period allows for considerable experimental investigation concerning the histogenesis of induced epidermoid carcinoma.

The path of absorption of chemical carcinogens can be studied by special techniques. It was found that when methylcholanthrene dissolved in benzene was applied to the skin of mice, it promptly made its way into the sebaceous glands and later spread to the intermitotic epidermal cells. The cells of the epidermis and of the hair follicles undergo malignant change much more frequently than do the intermitotic cells of the sebaceous glands, indicating that there is a greater "constitutional resistance" to the carcinogen by the cells which are affected first.

Painting the skin of new-born mice with the same carcinogenic agent does not result in malignant change. However, painting the skin of mice five days of age or older does result in epidermoid carcinoma. The difference between the skin of new-born mice and that of mice five days old is that the epidermis of new-born mice is thicker than that of older mice, and the hair follicles and sebaceous glands are either absent or rudimentary. By the fifth day of life, however, skin appendages form. These facts led Cowdry to conclude that the carcinogen needed a mode of entry in order for the epidermal cells to be affected and that the entry was through the pits supported by the hair follicles. In keeping with this thought, the experiments of Lacassagne and Latarjet showed that the skin of mice which had been freed of hair follicles and sebaceous glands by scarring was refractory to the carcinogenic action of methylcholanthrene, while the normal skin on both sides of the scar was not refractory.

Since there are no hair follicles in the oral mucosa, Levy and co-workers[7] attempted to determine the reaction of oral mucosa to a carcinogen by studying the comparative reaction of mucous membrane and skin in the lower lip of mice. The lower lip is ideally suited for such a study since the epithelium covering the skin side of the lip can be compared with the epithelium covering the mucous membrane side in the same section.

A carcinogen, dimethylbenzanthracene in benzene, was applied as a single application to the skin and mucous membrane surfaces of the lower lip of mice. Animals were sacrificed at regular intervals up to 32 days, and the lip was removed and sectioned in such a way that both the skin and mucous surfaces could be studied. The skin surface showed changes described by other investigators as typically precancerous, but the mucosal surface was completely refractory to the carcinogen. In additional studies, repeated painting of carcinogenic agents on the mucous membrane of the lip and tongue of mice and hamsters for periods up to six months verified the refractoriness of the oral mucosa to chemical carcinogenesis, but produced

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Intraoral Exfoliative Cytology

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Characteristic malignant squamous cells are shed from mucosal surfaces in the incipient stages of cancerous change prior to the conventionally accepted clinical signs. This allows for a modified form of tissue analysis by simply, quickly and atraumatically removing superficial cells for inspection. The most common cellular morphologic changes are those of pleomorphism, hyperchromatism and altered nuclear cytoplasmic ratio which reflect malignant change.

This technique has proven to be significantly accurate, there having been no false positives reported from thousands of slides, and the occurrence of false negatives having been no greater than those resulting from biopsy methods. However, it must be emphasized that cytology is an adjunct to and not a substitute for biopsy.

The value of cytology becomes most apparent in the puzzling evaluation of innocuous, nonspecific intraoral keratoses and ulcers, when cellular findings have indicated the necessity for biopsy and offered some basis for a combination of biopsy and surgical management. This technique has also been useful in evaluating lesions with previous negative biopsies where clinical suspicion still exists and in following treated patients for recurrence.

The following cases are discussed to illustrate the role of exfoliative cytology in early detection and early, adequate and proper management of intraoral carcinoma.

Case 1 — A 42-year-old white female was first seen a year ago for evaluation of a small, soft, lacy-white patch on the floor of her mouth overlying the left plica sublingualis (Fig. 1). Because of its innocent appearance, the patient was told to reduce cigarette smoking and return for further examination in three months. A checkup at that time showed no further change except for a slight inflammatory reaction at the periphery of the lesion and the patient complained of occasional burning in the floor of the mouth. The consultants felt that a further decrease in smoking, accompanied by palliative care, was adequate at this time. A routine cytologic smear (Fig. 2), however, revealed cancerous epithelial cells. Histopathologic slides from the 2 x 0.5-cm. specimen were unimpressive and read as "nonspecific inflammation with some reactive hyperplasia." However, the cytologic evidence prompted further investigation. Out of 417 sections eventually cut, 10 slides revealed carcinoma in situ with questionable early invasion of the underlying connective tissue (Fig. 3). The patient was referred for a more radical excision because of the vague and diffuse clinical inflammatory changes and the microscopic areas of multicentric reactive hyperplasia. Examination of the second surgical specimen did not reveal malignant change. This patient illustrates an instance where clinical judgment and experience proved insufficient. Without cytologic evidence, a more conservative program of observation and its concomitant delay would have dimmed the prognosis for this patient.

Case 2 — A 43-year-old white male came to the clinic for new dentures. He had been wearing his old dentures for over 10 years without any discomfort until recently he noticed that they were becoming slightly loose. A soft, freely movable 2-mm. ulcer with smooth, flat margins surrounded by a slight inflammatory response on the lower left alveolar ridge (Fig. 4) was noted. It was felt that this lesion represented a typical ulcer from denture irritation. There was certainly no indication at this time to perform any type of biopsy, and it was felt by the consultants that leaving out the denture and a palliative regimen of mouth rinsing combined with ointments was the therapy

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Fig. 1

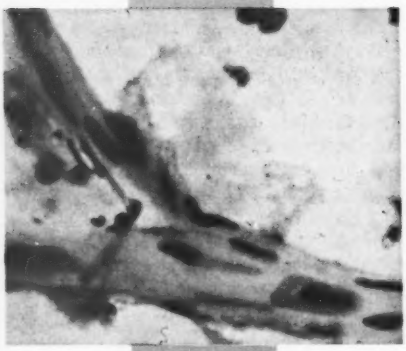

Fig. 2

Fig. 3

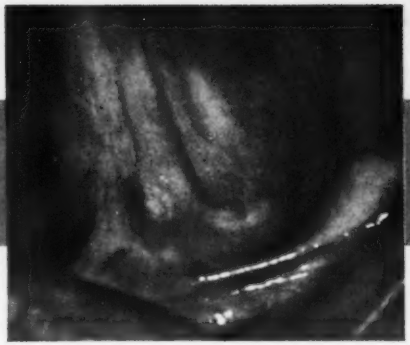

Fig. 4

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Fig. 8

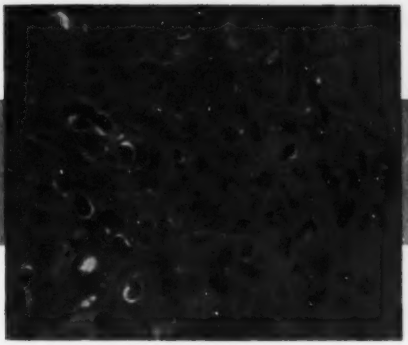

Fig. 5

Fig. 7

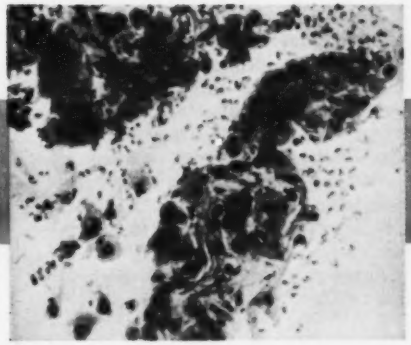

Fig. 9

Fig. 10

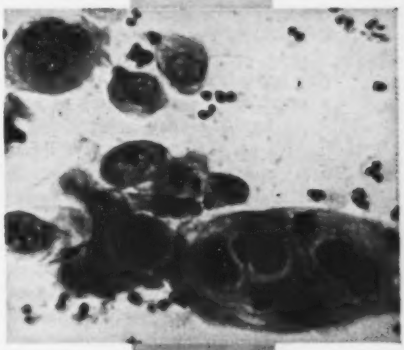

Fig. 11

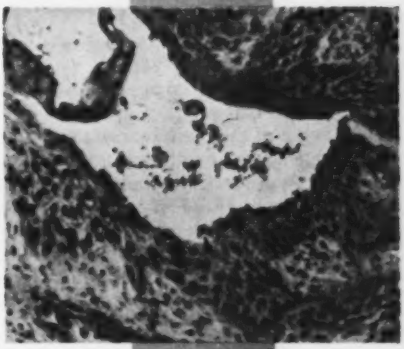

Fig. 12

to be followed while the new dentures were being made. Cancer cells were found at cytologic examination on this visit and later confirmed by biopsy. Excision with a half centimeter margin along with aggressive efforts to include periosteum, was accomplished in removing the lesion. Serial section showed intraepithelial malignant change. At a higher power (Fig. 5) the superficial malignant cells that were obtained cytologically were apparent. In all dimensions the margins seemed to be clear of any malignant or dyskeratotic changes. A review of the case at Tumor Board three weeks later led to a unanimous decision that the excisional biopsy had also accomplished the definitive surgery and that the cancer was probably completely eradicated. Subsequent clinical and cytologic examinations during the past year show no indications of a tendency toward recurrence.

Case 3 — A 48-year-old white man, who was a heavy cigarette smoker, noticed a white patch on the floor of his mouth (Fig. 6). A biopsy of the lesion, taken from a suspicious area by a local physician, showed no malignant activity. The patient was referred for cytologic examination because the lesion would not heal and carcinoma was suspected. Smears from the lesion displayed cellular features of clumping, pleomorphism, hyperchromatism, enlarged nuclei and abnormal clearing. Because of the observed malignant cells, wide excision under general anesthesia was advised. The surgical specimen (Fig. 7) revealed squamous cell carcinoma. This case illustrates that a single incisional biopsy may not be representative or adequate to rule out malignant activity.

Case 4 — A 61-year-old white man was examined after an apparently successfully treated excision of a squamous cell carcinoma of the right floor of the mouth. The patient was asymptomatic and there was no evidence of lymphatic spread. Intraoral examination (Fig. 8) revealed some scanty, soft, freely movable, apparently innocuous keratotic changes overlying the unimpressive surgical scar tissue. Poor hygiene probably accounted for inflammation about the area. The patient was progressing well and was told to return in three to six months. However, routine cytologic smears (Fig. 9) of this area revealed cells consistent with malignant recurrence. This evidence was sufficient to support a re-excision of this area. The surgical specimens confirmed the cytologic evidence of malignant neoplasia. The patient has been subsequently followed for two more years without further evidence of tumor activity. Cytologic evidence in this case has without much doubt extended the period free from recurrence.

Case 5 — A 48-year-old white female was referred to the clinic by her physician because of an asymptomatic intraoral lesion of two weeks duration. Clinical examination revealed a soft, freely movable 3-mm. mass in the area of the orifice of the right Wharton's duct (Fig. 10). The overlying erythematous mucosa had a slight degree of keratosis without ulceration. There appeared to be some saliva being excreted from the duct and the patient reported no swelling of the right submandibular gland. There were no palpable or tender lymph nodes. Impressions at this time included trauma, a collapsed cyst, or calculus in the duct. Since biopsies are not without complications in this area, there was a strong tendency to consider palliative therapy and other less traumatic diagnostic procedures. A cytologic smear (Fig. 11) during this examination revealed cells consistent with malignancy. At this time, then, not only was biopsy indicated but an excision with wide and aggressive margins. This was accomplished the next day under local anesthesia. Serial sections (Fig. 12) revealed a very early squamous cell carcinoma with adequate borders in all dimensions. This patient has now been followed for over two years without evidence of recurrence. Wharton's duct has established drainage slightly distal to the normal anatomical area and the operated area is completely asymptomatic. This case again illustrates the advantages of the cytologic technique for the early detection and judgment in the biopsy management of malignant change.

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carcinoma of the perioral skin. Kolas was also unable to produce carcinomas of the oral mucosa of mice, and Van Prohaska et al. reported only one carcinoma of the oral mucosa of mice fed methylcholanthrene in olive oil over a period of six months. The carcinoma in this animal occurred in the cheek.

Explanations for the refractoriness of the epithelium of the oral mucosa are difficult but important. One might suggest that the saliva or other oral fluids act as an inhibitor or protective substance in intraoral carcinogenesis. Goldhaber, in investigating this aspect of the problem, found that surgical removal of the major salivary and lacrimal glands of mice did not significantly alter the resistance of the labial mucosa to a carcinogen, although desalivation apparently enhanced the occurrence of perioral skin tumors. He also found that a few mice surviving 10 to 12 months after desalivation showed early intraoral carcinoma. These changes were associated with ulceration probably caused by continuous trauma of food and hair impaction. The simple desalivation or removal of the major salivary glands did not rule out the fact that the numerous minor salivary and mucous glands of the oral mucosa still functioned, and these might have provided a protective mechanism and increased resistance of the cells to carcinogenic action.

Kreshover and co-workers have added to the concept of cellular resistance of oral mucosa by exposing the mucocutaneous region of the lips of mice to tobacco smoke each day for 76 weeks. They found that the lip region was unaffected, and that neither the sex of the animal nor a deficiency of vitamins A and B had any influence on its resistance. On the other hand, the ears of the mice were noticeably affected by the same treatment directed to the ear. Ulceration, hyperkeratosis and hyperplasia were manifested early, and precancerous lesions developed after 17 months of treatment. They also found that the palatal tissues of hamsters were unaffected by either daily exposures to tobacco smoke or triweekly exposures to a chemical carcinogen, but that the cheek pouch showed inflammatory changes following tobacco smoke application, and carcinoma following benzpyrene application.

Goldhaber also studied the localization of 3-methylcholanthrene by means of fluorescence microscopy in the skin and mucous membrane sides of the lower lip of mice and monkeys. He found that on the skin surface the fluorescence of the carcinogen was localized primarily within the sebaceous glands, while on the mucosal side the fluorescence of the carcinogen was restricted to the outermost layers of the oral epithelium and the keratin.

Levy[6] has studied the effects of injecting methylcholanthrene beneath the mucous membrane of the tongue of mice. This type of application produced carcinoma of the tongue in a large number of animals. These findings lend some support to the "portal of entry" theory of Cowdry and others.

The ameloblastoma of the jaw has always been an intriguing tumor. The incisor tooth of the rodent is a persistently growing tooth, so that there is undifferentiated epithelium as well as undifferentiated mesenchymal tissue at its apex. This is a unique situation in which one finds embryonic cells, with all of the problems of induction and organization, persisting in and surrounded by adult tissue. Studies of the effects of carcinogens on these cells might prove interesting, especially in view of Needham's thoughts concerning the inter-relationships of organizers and cancer. Needham believes that one of the most important aspects of cancerous growth is that it is an escape from the organizer influence.

Using hamsters and mice, Levy and Ring[8] surgically exposed and treated with methylcholanthrene or dibenzanthracene the growing end of the lower incisor tooth. The animals were observed for periods up to one year. Serial sections of tumors, as well as of jaws of animals without tumors but treated and sacrificed at various intervals, were made, and the response of the embryonic tissue was studied. Some tumors were produced. In hamsters these were sarcomas of either fibrous tissue or

of muscle, while in mice they were osteogenic sarcomas. No ameloblastomas developed.

In order to explain the reaction of the undifferentiated pulp tissue to this procedure, some understanding of cell types is necessary. Cells are classified as intermitotic or postmitotic types. The intermitotic cells are either those which are capable of differentiating into cells of a higher level, or vegetative types of cells which divide and then differentiate, such as a basal epidermal cell. The differentiating intermitotic types would be cells such as the spinous cells of the epidermis which develop from cells of the vegetative type but can be distinguished from them. The postmitotic cells, on the other hand, discharge their function and then die (fixed postmitotic), or they discharge their function and revert to an intermitotic form (reverting postmitotic). The two kinds of intermitotic and the reverting postmitotic cells have potentially malignant properties. Ameloblasts perform their function, revert to a squamous type of epithelium and then die. These may be considered, then, as falling between the fixed and the reverting postmitotic types of cell; therefore they have a limited potential for malignant change. More must be known concerning the biology of these cells, however, before one can explain their resistance to carcinogenic agents.

The physiology of the oral mucosa and its appendages is of great importance to the field of biology in general and specifically to cancer research.

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Squamous Cell Carcinoma of the Gingiva

It is evident that chronic irritation predisposes to leukoplakia and carcinoma. Studies of smoking cigarettes, pipes and cigars have shown that the burning coal is at 400° C. This high temperature may fractionate hydrocarbons in the tobacco and produce carcinogens in the smoke. The smoke as it enters the mouth is at about 37° C.

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Diagnosis of Oral Cancer Including Indications and Procedures for Biopsy

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All lesions of the oral cavity should be positively identified as to their specific cause and character so that positive definitive therapy can be directed toward their elimination and cure. To achieve this goal it is necessary to have all the information available about the patient and his disease.

History

The first step in obtaining necessary knowledge about the patient and his disease is the taking of a detailed history which should include his chief complaint, present illness and past medical and dental history. The history should include detailed information regarding events leading to the development of the lesion, the initial character of the lesion and any changes which occurred as it developed. It should also include any symptoms which attended the development and progress of the lesion. These facts should be recorded in chronologic order indicating the time elapsed from initial recognition to the present. The obtaining of a complete history should be followed by a detailed examination of the neck, face and oral cavity.

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Examination

The clinical examination of the patient should be of such a nature that it will enable the examiner to identify the cause of the disease for which the patient seeks help and to detect disease which is unknown to a patient who is apparently well. This examination can be accomplished only by following an orderly procedure of inspection, palpation, percussion and sometimes auscultation. These procedures should progress in an orderly and routine manner so that all areas are examined.

Face and neck. The approach to such an examination starts by observing the face of the individual for any asymmetry that may be produced by a tumor or swelling. The skin of the face and neck should be observed for evidence of change in color, texture, scars and absence of hair. The

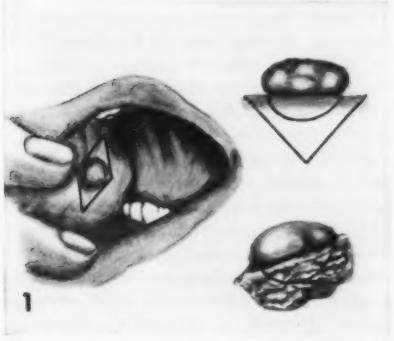

Figure 1. Excisional biopsy of soft tissue lesion. Heavy line in basal tissue indicates the estimated clinical depth of the lesion.

Figure 2. Incisional biopsy of soft tissue lesion. Representative area and transition zones to normal tissue are included in the specimen.

neck should be examined for scars, swellings and changes in the skin. These observations should be followed by palpation of the cervical lymph nodes with attention given to each group independently. The major salivary glands and the thyroid glands as well as the lymph nodes should be palpated for evidence of enlargement or firmness. The jaws also should be examined for any limitation or abnormal pattern of movement, and any alteration in contour of the jaws should be determined by palpation.

Oral cavity. With these observations completed the examiner next should move to the oral cavity with the lips being the first area to receive attention. The vermilion border should be examined for evidence of atrophy, indicated by loss of vertical markings, and for color and texture. Minor changes in texture and color result from exposure to sunlight and weather. The lip is smooth, shiny or may have a slight tendency to desquamate flakes of keratin. A whitish-blue color and slight opacity are the initial changes, but these changes may progress with the lip being white and opaque. The repeated appearance of superficial ulcers which heal slowly may be seen also. These changes from exposure are seen in older patients, those who spend much time out of doors and those with very light complexions. The changes in the lip are designated as solar cheilitis or senile cheilitis and are precancerous in character. A large number of patients who have carcinoma of the lip develop it on the basis of solar cheilitis. Patients with minor changes should be warned of the presence of these changes and instructed in methods of protection of the lips to prevent more severe changes.

The vestibular mucosa should next be inspected and palpated. The palpation should be bidigital and will thus include the lip. The cheeks should now be reflected and the buccal mucosa, including the mucobuccal gutter, inspected. Palpation of the buccal mucosa should be bimanual which permits the examination of the full thickness of the cheeks. It also permits the expression of saliva from the parotid duct so that salivary flow can be evaluated. The tongue should be elevated to view the floor of the mouth and the under surface of the tongue. Palpation of the floor of the mouth should be bimanual to elicit any lesions which are located deep in the tissue. Bimanual pressure permits observation as to patency of the submaxillary and sublingual ducts and the quality of secretion. The dorsum of the tongue and lateral borders should be examined by pulling the tongue forward to its full limits and then moving it to the right and left so that its lateral borders and its attachment in the posterior areas may be examined by both inspection and palpation. The tongue should also be depressed to permit inspection of the pharynx.

The examiner should next inspect the palate for alteration in contour. It should also be palpated for evidence of swelling or areas of softening due to bone destruction. The teeth should be examined for evidence of mobility, sharp, irregular cusps and evidence of periodontal disease. If teeth show increased mobility, the gingival sulcus should be probed to determine if pockets are present and if bone loss is sufficient to account for the increased mobility.

After the clinical examination of the oral cavity, the jaws should be examined by full mouth periapical x-ray films. This examination will visualize most lesions of the jaws, but these films may have to be supplemented by lateral jaw or occlusal films.

If this procedure of oral examination is followed, all the areas of the mouth will be inspected and any lesion will be detected. After detection of a lesion, it should be examined in detail to determine its nature and cause if possible. If positive diagnosis cannot be made by clinical examination, auxiliary aids may have to be used. It may be necessary to carry out various clinical laboratory procedures such as hematologic, bacteriologic and histologic studies. Tissue study of a biopsy specimen is the most frequently used auxiliary procedure. It provides valuable information as to the nature of the disease process and its etiology. It may be of value also in dictating therapy. Numerous lesions of the

oral cavity may not present sufficient specific clinical characteristics for diagnosis, and biopsy is indicated. Lesions are presented here as characteristic types which may require biopsy for definitive diagnosis. They are presented to illustrate points in differential diagnosis and to demonstrate biopsy techniques for lesions of various types and locations.

Biopsy Procedure

Criteria for biopsy. The decision to utilize biopsy procedure in diagnosis of mouth lesions exemplifies the responsibility accepted by dentists for preservation of oral health. The clinical impression that a specific tissue area "does not look right" or the failure of the more common inflammatory processes to follow an expected course of healing will propose a need for biopsy. "Watchful waiting" and "periodic observation" carry dangerous pitfalls. Potential tragedy from procrastination is illustrated by the progressive and insidious course of a painless malignant neoplasm. In addition to the detection or "ruling out" of neoplastic tissue changes the biopsy procedure is important for the identification of specific infectious processes, reactive lesions and certain metabolic disorders. Specifically, lesions indicate biopsy investigation if (a) an ulcer persists for two to three weeks without evidence of healing; (b) definite persistent hyperkeratotic changes are found in surface tissues; (c) any persistent tumescence is visible or palpable beneath relatively normal surface tissues; (d) inflammatory changes persist for prolonged periods; (e) bone lesions are not identified specifically by clinical and x-ray findings.

Goals of biopsy. Since the goal of biopsy procedure is to obtain representative tissue in nearly its "in-vivo" state for microscopic study, the techniques must be specific and performed with care. The histologic changes interpreted by the pathologist can be accurate only if the quality of the tissue specimen has preserved cellular detail. For this reason the preferred method of obtaining tissue is sharp, cold scalpel excision with minimal crushing and manipulation. Tearing and mutilation of the specimen are avoided. Distortion of tissue by antiseptic dyes such as iodine and mercurial preparations should be avoided. Topical anesthetics are not used in the area and local anesthetic solution is not injected directly into the biopsy site. Gentle removal of the excised specimen further avoids distortion. Immediate immersion in fixing solution of 10 per cent formalin in a wide mouth bottle prevents changes of drying and autolysis. Ample formalin solution, 20 times the volume of the specimen, assures complete fixation. Leakproof caps for the specimen bottles and protective mailing containers ensure safe transport of the material to the laboratory. A secure label on the bottle identifies the patient's name, the date of biopsy and the name of the operator.

The limitation of any pathologist's interpretations of isolated histopathologic characteristics of a specimen is obvious. The clinician should provide an adequate history and clinical description of the lesion. The exact location and gross clinical features may be further described by the assistance of diagrams. If there is associated involvement of bone, roentgenograms sent with the specimen may be helpful. If all of these salient data are available to correlate with microscopic features, the pathologist is assisted to more accurate interpretation of his microscopic findings. It is also evident that superficial specimens, necrotic tissue and crusts have little value for the pathologist's study and interpretation.

Office procedure. The dentist is amply prepared in anatomy and basic surgical principles of the mouth and jaw region to perform biopsy procedures as an aid to diagnosis. The techniques are painless and simple, and the armamentarium is readily available in the dental office.

Removal of soft tissue specimens require: (a) local anesthetic equipment, (b) sharp scalpel and scissors, (c) fine tissue forceps, (d) hemostat forceps, (e) needle holder, (f) gauze sponges, (g) suture and needle.

Removal of bone specimens will necessi-

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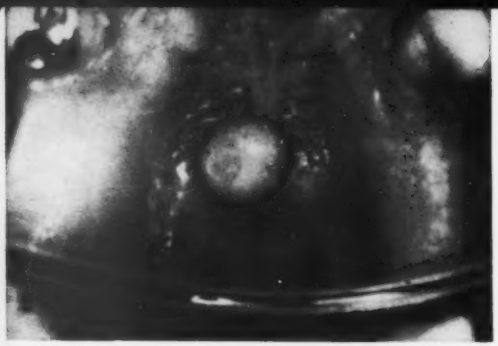


Figure 3. A painless firm nodule in the midline of hard palate mucosa had developed in contact with a prosthetic appliance bar. Growth had been slow and the pedunculated formation presented sessile features with a narrow stalk base. A common reactive lesion, the post-traumatic fibroma, was excised locally to the periosteal basal tissues.

Figure 4a. Palatal tumescence with distended mucosa which developed gradually over an eight-month period without significant symptoms. The patient, a 35-year-old nurse, sought dental treatment regarding the maxillar left first molar. The tooth was found to be devital.

Figure 4b. Radiograph of the left maxillary region. In addition to the maxillary sinus a radiolucent zone is suggested in the area of the first molar palatal root. Among differential diagnostic possibilities suggested: subperiosteal extension of odontogenic chronic inflammatory process, fibroma, lymphoma and mixed tumor must be included. The first molar was extracted. No penetration of bone could be demonstrated at the apex of the palatal root alveolus. The tumescence was then excised with inclusion of the underlying periosteum. Cortical bone of the hard palate was depressed beneath the tumor but was not invaded.

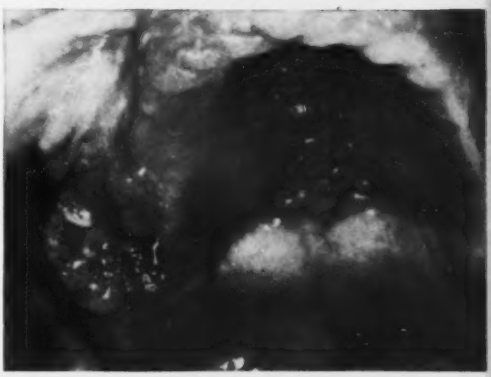
Figure 4c. Excised encapsulated benign mixed salivary gland tumor.

Figure 5. A 45-year-old white male presented with greyish-white hyperkeratotic lesions of the lower lip, gingiva and buccal mucosa. The buccal lesions were stellate, slightly elevated and beaded. The gingival lesions were plaque-like. The lesions on the vermilion were plaque-like and there were fine striae. Some of the features suggested lichen planus, but the plaque-like lesions of the lip were slightly firm and more hyperkeratotic than is characteristic of lichen planus. The plaque to the left of the midline was removed for biopsy. The excisional procedure removed the entire lesion and verified the diagnosis of lichen planus.

Figure 6. Nonpainful ulcer of the vestibular mucosa at the commissure present for two months in a 60-year-old male. A sharply circumscribed ulcer, with some pearly elevations of the border, which has shown gradual increase in size. There is induration of the base which extends outside the zone of ulceration and is indistinct to palpation. The possible differential considerations are: squamous cell

carcinoma, periadenitis mucosae, necrotica recurrens, traumatic ulcer and mycotic infection. The size and location of the lesion does not present easy total excision. Incisional biopsy would provide an adequate specimen for microscopic diagnosis and would leave enough residual lesion to designate its location and character if further treatment is indicated. An ellipse of tissue extending from the center of the lesion across the border for the full depth of the lesion removed by sharp cold steel dissection provided an adequate specimen completely representative of the lesion. The histological diagnosis rendered on the incisional biopsy specimen was cornifying squamous cell carcinoma.

Figure 7. A 78-year-old white female consulted her dentist because her dentures did not fit. She had been having trouble with them for several months. She had worn dentures for 25 years. During the past two years she had been hospitalized on four occasions; the last time three weeks previous to presenting to her dentist. Her dentures had not been removed and her mouth inspected at the time she was in the hospital. Inspection of her mouth revealed an ill-fitting denture. The mucosa of the palatal vault was red and somewhat soft. The surface was composed of numerous confluent nodular masses. Over the right tuberosity was a fungating lesion with a necrotic center which protruded from beneath the heel of the denture. A definite indentation could be seen where the heel of the denture contacted the mass. The lesion was firm and the boundaries indistinct. Differential diagnosis was between a squamous cell carcinoma and a sarcoma. With an electric scalpel a portion of the mass was excised. The cauterization which resulted made it unnecessary to suture the wound. The changes in the palatal vault were typical of palatal papillomatosis but because of the presence of the other lesion it was desirable to verify this with an excisional biopsy. This also was done with an electrosurgical scalpel. The lesion of the tuberosity was squamous cell carcinoma and the palatal change was reactive.



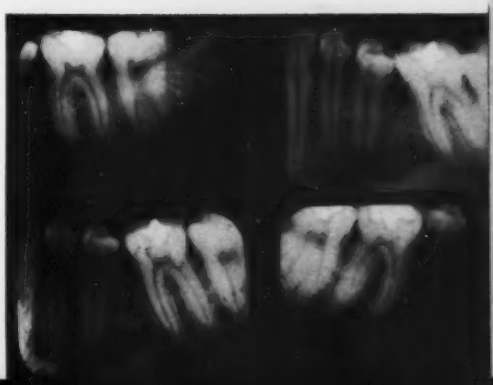


Figure 8. X rays demonstrating a small lytic zone in the area of the right mental foramen of the mandible. These features were not diagnostic but the history was most significant. A 14-year-old schoolgirl complained of pain in the right mandible for three weeks. Careful examination of the teeth was negative and all teeth were vital. Symptoms then changed to paresthesia and anesthesia in the distribution of the right inferior alveolar nerve and mental branches. Biopsy of this zone of the alveolar process yielded the alarming diagnosis of neurofibrosarcoma.

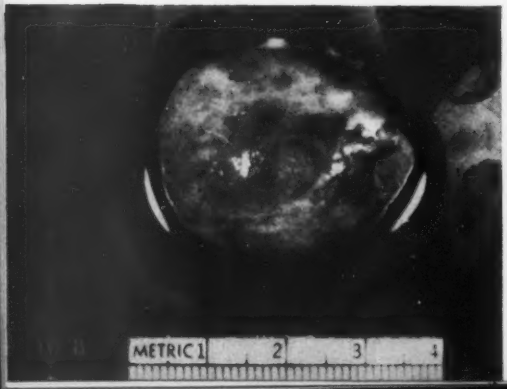
Figure 9. Ulcerated, slightly tender lesion on dorsum of tongue, of a 15-year-old boy, which has been present for four weeks. Slightly elevated ulcerated lesion with distinct border. There is some induration in the base which is sharply localized although slightly indistinct. In differential diagnosis granuloma pyogenicum, mycotic infection, traumatic ulcer and neoplasia would have to be considered. Biopsy was indicated. Due to the small size and character of the lesion, its total excision was indicated rather than partial excision. The total lesion then became the biopsy specimen. The residual defect can be handled more easily with total excision than with partial excision, and treatment is final. The microscopic diagnosis was granuloma pyogenicum.

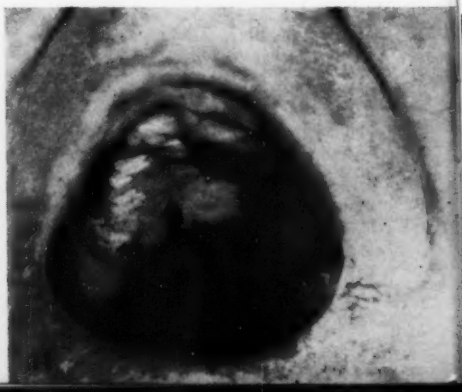
Figure 10a. The large tumescence obliterating the right buccogingival sulcus and extending over the alveolar ridge had enlarged gradually over several years. Although distended, the overlying mucosa had a normal surface and the mass was freely mobile in the tissues of the cheek. The area was moderately soft and not tender to palpation. Definite encapsulation was suggested. Differential diagnostic considerations included: inclusion cyst, lipoma and mixed tumor.

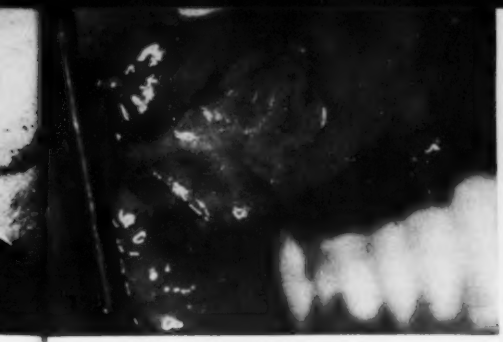
Figure 10b. Excised encapsulated lipoma specimen of clinical lesion shown in Fig. 10a.

Figure 11. A 60-year-old white female who has worn dentures for 25 years. For an unknown time there had been a white lesion on the crest of the ridge and the palatal vault. This was asymptomatic. Inspection and palpation revealed a white, tough, leather-like, rough, slightly elevated lesion which is firmly attached to the underlying mucosa. Incisional biopsy with one specimen from the ridge in the molar region and one at the summit of the palatal vault indicated a Grade I squamous cell carcinoma. Carcinomatous change over a wide area of the palatal mucosa is associated with the wearing of dentures.

Figure 12. Nonpainful ulcer of the buccal mucosa of a 45-year-old white male which had been present for several months with gradual increase in size. The patient, a heavy smoker, showed evidence of nicotine stomatitis and presented a large, irregular, shallow ulcer with a slightly greyish granular base and extensive inflammatory border. The base of the ulcer is slightly firm but indistinct. In differential diagnosis squamous cell carcinoma, chemical burn, traumatic ulcer and mycotic infection must be considered. Inci-







sional biopsy is indicated in this instance because of the size of the lesion. An ellipse of tissue was sharply excised with a cold steel scapel extending from within the lesion across its border into normal tissue. This provided an adequate representative specimen with a residual defect which was easily closed with two or three interrupted sutures. The histological diagnosis was squamous cell carcinoma.

Figure 13. A 60-year-old white male complained that a "bump" in his cheek prevented him from comfortably holding his tobacco quid in the accustomed place. He had no other complaints referable to the lesion and was not sure how long it had been present. Inspection revealed an exophytic, granular, indurated lesion of the buccal mucosa which on palpation definitely infiltrated the buccal mucosa. The lesion was most suggestive of a carcinoma which was verified from the biopsy. Incisional biopsy extending from the center across the anterior border provided the biopsy specimen. The sutures used to close the biopsy site can be seen in the photograph.

Figure 14. A soft, deep tumescence in the submental area had progressively developed over several years and appeared to fluctuate slightly in size. Inspection and palpation indicated central location between mucosa of the floor of the mouth and submental skin surface. There was no regional or generalized lymphadenopathy. Diagnostic clinical impressions included cyst variants, angioma, lipoma and other soft tissue neoplasms with possible central liquefaction. Diagnostic aspiration with 20-gauge needle yielded amber-colored flocculent fluid from an inclusion cyst of epidermoid variety which was subsequently enucleated.

Figure 15. An asymptomatic papilliferous firm lesion involving the palate and the alveolar process of a 35-year-old female. This is a recurrent lesion following the removal of a smaller lesion several years previously. This recurrent lesion has shown a gradual slow increase in size with progress of the papilliferous character. Differential diagnosis must consider: benign neoplasm of fibrous, glandular or neurogenous origin, papillomatous hyperplasia and varieties of mixed tumor. An elliptical piece of tissue from the papillomatous area and a wedge of tissue from the tuberosity were excised for microscopic examination. The tissue changes were of the same character in both areas and verified the diagnosis of fibroma.

tate the addition of: (a) periosteal elevator, (b) bone chisel and mallet, (c) bone drills, (d) curettes.

Aspiration of specimen material will require only a 10 ml. sterile syringe and an 18 gauge needle.

Application of Technique to Various Types of Lesions

Soft tissue lesions. Generally the entire lesion completely excised with borders in normal tissue at peripheral margins is the most desirable specimen for the patient, the surgeon and the pathologist. Therefore, small lesions (less than 1 cm. in diameter) located in noncritical anatomic zones are best excised completely as the biopsy procedure (Fig. 1). Encapsulated lesions also are completely excised. Since this is therapeutic excision in most instances, adequate depth and margins into normal tissue become essential to the procedure. The responsibility for complete excision, therefore, must be acknowledged. In the lesions shown in Figures 3, 4a, 9 and 10a, excisional biopsy was indicated.

Larger lesions or those that are located in significant functional anatomic zones are approached by incisional biopsy technique. The specimen site selected is representative of the complete tissue changes and extends through normal tissue at the base and margin of the lesion (Fig. 2). Variation in lesion features may indicate need for several representative specimens which are carefully identified by diagram and placed in separate bottles. Thin sections may be kept flat by support on a block of gelatin sponge. Similarly material obtained by aspiration or curettage may be oriented on a block of gelatin sponge before placing into fixing solution. In this manner the handling and orientation of material are facilitated.

Keratotic lesions. Surface changes of a white-patch character are commonly seen on oral mucosal surfaces. The first clinical investigation of such areas is gentle wiping of the area with cotton or gauze. This wiping will dislodge superficial epithelial desquamation and plaques of moniliasis. Focal areas of hyperkeratosis may have obvious association with local irritation. If the local irritation is completely eliminated, regression of the keratotic change may be observed over a two-week period. Such areas should be kept under close surveillance until the surface has returned to normal features. Any ulceration, verrucous thickening or cracking in a zone of hyperkeratosis indicates immediate biopsy. A persistent hyperkeratotic zone after the removal of irritants will warrant biopsy without these specific danger signals. If the microscopic description includes dyskeratotic changes of leukoplakia, the involved mucosal surface should be removed. Excision of such areas by stripping at a submucosal level is effective (Fig. 11). Relatively large areas of surface tissue may be excised in stages by this method. The involvement of the vermilion mucosa of the lip in severe solar cheilitis is effectively managed by this method (Fig. 5).

Once the pathologic diagnosis of leukoplakia without definite malignant change has been made, superficial destruction of the white-patch area may be accomplished by fulguration. Epithelial regeneration will resurface the zone treated in this manner. Such destructive procedures will be unnecessary for lichen planus and other white lesions without significant dyskeratotic (precancerous) connotation.

Ulcerative lesions. Surface loss of ulcer formation is the most common mucosal lesion; it follows trauma and infectious processes. Biopsy, therefore, is limited to selected lesions with definite suspicious characteristics (Fig. 6). Absence of healing potential, peripheral hyperkeratotic changes, elevated margins and indurations are a few of the findings which arouse suspicion. The size and location of the lesion will determine whether the excision or incision technique of biopsy is used (Fig. 12).

Proliferative lesions. The protruding lesion may be represented by reactive conditions following trauma, by specific infections or by neoplasms (Fig. 13). X-ray diagnosis of underlying osseous tissue frequently is helpful. Excisional or incisional

biopsy will be selected on the basis of the size and location of the lesion (Fig. 7).

Nodules or papillomas. The isolated, elevated lesion without loss of surface tissue is best appraised by palpation. The depth of subsurface extension may thus be estimated and the excision margins planned accordingly. In some instances traction of the lesion will elevate tissues at the base in order to facilitate complete excision. Large areas of papillomatous tissue involvement will warrant preliminary incisional biopsy (Fig. 15).

Tumescences. The tumescent mass of apparently noninflammatory origin is best approached with caution. Preliminary palpation may estimate the size and consistency of the mass. When lymph node changes and chronic abscess processes are not likely, the probabilities are in the realm of cystic or neoplastic lesions. Aspiration of a deep unknown mass is helpful as a preliminary procedure (Fig. 14). Cystic fluid has recognizable characteristics, and fluid from a degenerating malignant neoplasm may yield significant cells for study by the pathologist. The pitfall of a large hemangioma is also avoided by preliminary aspiration. Some cysts of epidermoidal inclusion type will contain solid material which fails to aspirate through a large needle. If the mass is of significant size, any surgical biopsy procedure is best postponed until complete excision may be accomplished under optimal operating-room conditions.

Intraosseous lesions. Biopsy of bone lesions is used after x-ray and other laboratory data have not yielded diagnostic certainty. The cortical bone over the lesion is exposed by reflection or mucoperiosteal flap for adequate access. Preliminary aspiration of such intraosseous lesions is always a good policy. If the cortex cannot be penetrated by a heavy needle, a bone drill may be used to reduce the thickness of the lateral wall. This precaution will detect the possible intraosseous hemangioma or arteriovenous fistula which might present acute problems in hemorrhage control. When this precaution has been satisfied, better access may be obtained with removal of the cortex over the lesion to obtain a central tissue specimen by curettage (Fig. 8).

Judgment in Biopsy Procedure

Technical aspects of biopsy procedure applied to a variety of types of lesions require some modification of judgment. If there are strongly suspicious signs of malignancy revealed in clinical examination, the dental practitioner will contribute little by performing a biopsy and may distort the lesion or delay urgent treatment. If the clinical suspicion of malignancy is strong, manipulation of the lesions should be avoided. The problems of metastasis and the limitations of known methods to eradicate malignant processes require urgency of prompt action by a qualified therapist. Immediate referral to a cancer treatment center will be the best service to the patient. When the gross clinical features of a lesion have suggested squamous cell carcinoma, there is no advantage in having the dentist undertake the biopsy. He may lack experience in biopsy procedure. He has made the important decision that diagnosis and treatment are urgent; he then may determine the best qualified consultant available. When the appointment has been made, he may accompany the patient for the consultation visit. A concern to be sure that the patient has obtained proper attention is an important responsibiilty of the dentist.

On the other hand, many lesions of questionable significance arouse suspicion and deserve biopsy investigation. The presentation of the biopsy procedure to a patient requires practical psychology. It is possible to alarm a patient with cancerophobia to despair by the mere suggestion of a biopsy without adequate explanation.

When benign processes are reported by the pathologist, the clinician cannot be lulled into complacency. It is always the clinical course of the disease, not the pathologist's report, that determines ultimate prognosis. If healing is not complete or if suspicious signs persist in the area of biopsy, a repeat investigation is indicated with additional biopsy. It is only after healing has returned to normal that the process can be considered eliminated.

SYMPOSIUM ON EVALUATION OF

SCIENTIFIC PROGRAM OF THE AMERICAN CANCER SOCIETY,

Monday, October 26, 1959
Morning Session—9:00 A.M.

CHAIRMAN:
Dr. Calvin T. Klopp
George Washington University
School of Medicine
Washington, D. C.

The Purpose of the Meeting
Dr. Eugene P. Pendergrass
University of Pennsylvania
School of Medicine
Philadelphia, Pa.

What is Early Cancer?
Dr. Danely P. Slaughter
University of Illinois
College of Medicine
Chicago, Ill.

What Is an Adequate Cancer Checkup?
Dr. Emerson Day
Memorial Center for Cancer
and Allied Diseases
New York, N. Y.

The Changing Responsibility of the Practicing Physician
Dr. I. Phillips Frohman
Washington, D. C.

Panel: The Economics of Cancer Detection

Moderator:
Dr. John W. Cline
Stanford University School of Medicine
San Francisco, Calif.

Participants:
Dr. Leona Baumgartner
Commissioner of Health
New York, N. Y.
Dr. R. Lee Clark, Jr.
M. D. Anderson Hospital and Tumor Institute
Houston, Texas
Dr. H. L. Kottmeier
Radiumhemmet
Stockholm, Sweden
Drs. Day, Frohman, Klopp, Pendergrass, and
Slaughter

Monday, October 26, 1959
Afternoon Session—1:30 P.M.

CHAIRMAN:
Dr. Ashbel C. Williams
St. Vincent's Hospital
Jacksonville, Fla.

DETECTION VALUE OF PERIODIC EXAMINATIONS

Early Cancer of Colon and Rectum
Dr. Ralph E. Hertz
Memorial Center for Cancer and
Allied Diseases
New York, N. Y.

Early Cancer of Uterine Cervix
Dr. Charles L. Easterday
Harvard Medical School
Boston, Mass.

Early Head and Neck Cancer
Dr. Grantley W. Taylor
Massachusetts General Hospital
Boston, Mass.

Early Cancer of the Breast
Dr. Edward F. Lewison
Johns Hopkins University School of Medicine
Baltimore, Md.

Early Genitourinary Cancer
Dr. Roger Baker
Georgetown University School of Medicine
Washington, D. C.

Early Cancer of the Stomach
Dr. Owen H. Wangensteen
University of Minnesota Medical School
Minneapolis, Minn.

Early Lung Cancer
Capt. Robert B. Brown
U. S. Naval Hospital
Bethesda, Md.

Panel: Does Periodic Examination of Well Persons Increase Longevity?

Moderator:
Dr. Robert M. Zollinger
Ohio State University College of Medicine
Columbus, Ohio

Participants:
Drs. Baker, Brown, Easterday, Hertz, Lewison, Taylor, Wangensteen, Williams

EARLY DIAGNOSIS OF CANCER

BILTMORE HOTEL, NEW YORK CITY, OCTOBER 26-27, 1959

Tuesday, October 27, 1959
Morning Session—9:00 A.M.

CHAIRMAN:

Dr. Frank W. Foote, Jr.
Memorial Center for Cancer
and Allied Diseases, New York, N. Y.

The Problem of the Precancerous Lesion
Dr. Fred W. Stewart
Memorial Center for Cancer
and Allied Diseases, New York, N. Y.

The Problem of the 7 Danger Signals
Dr. E. Cuyler Hammond
American Cancer Society Inc.
New York, N. Y.

PRECANCEROUS LESIONS AND HOW TO TREAT THEM

Breast
Dr. Murray M. Copeland
Georgetown University School
of Medicine, Washington, D. C.

Skin
Dr. Francis W. Lynch
University of Minnesota Medical School
Minneapolis, Minn.

Oral Leukoplakia
Dr. William S. MacComb
M. D. Anderson Hospital and Tumor Institute
Houston, Texas

Uterus
Dr. John B. Graham
Roswell Park Memorial Institute
Buffalo, N. Y.

Stomach
Dr. Russell S. Boles
University of Pennsylvania
School of Medicine, Philadelphia, Pa.

Rectum and Colon
Dr. Michael R. Deddish
Memorial Center for Cancer and
Allied Diseases, New York, N. Y.

Thyroid
Dr. Thomas J. Anglem
Boston University School of Medicine
Boston, Mass.

Moles
Dr. George T. Pack
Memorial Center for Cancer
and Allied Diseases, New York, N. Y.

Tuesday, October 27, 1959
Afternoon Session—1:30 P.M.

CHAIRMAN:

Dr. Glenn H. Leak
University of Buffalo
School of Medicine
Buffalo, N. Y.

The Value of Staging and Proper Reporting
Dr. R. Lee Clark, Jr.
M. D. Anderson Hospital and Tumor Institute
Houston, Texas

THE TREATMENT OF EARLY CANCER

Breast
Dr. Jerome A. Urban
Memorial Center for Cancer
and Allied Diseases, New York, N. Y.

Larynx
Dr. Edgar L. Frazell
Memorial Center for Cancer
and Allied Diseases, New York, N. Y.

Cervix
Dr. Howard Ulfelder
Harvard Medical School
Boston, Mass.

Rectum
Dr. Neil W. Swinton
Lahey Clinic
Boston, Mass.

Skin
Dr. Kenneth L. Pickrell
Duke University School of Medicine
Durham, N. C.

Thyroid
Dr. John C. McClintock
Albany Medical College
Albany, N. Y.

Oral Cavity
Dr. Arnold J. Kremen
University of Minnesota Medical School
Minneapolis, Minn.

new developments in cancer

Yeast Polysaccharides . . .

I. C. Diller and Z. T. Mankowski (Philadelphia) have used relatively nontoxic polysaccharides from yeast (C. Guilliermondi) and symosan from saccharomyces against mouse sarcoma in vivo and in vitro. Cells which took up the polysaccharide particles in vitro were destroyed; those that didn't were unharmed. The materials produced temporary tumor regressions when injected into mouse bellies or veins. Because the polysaccharides stimulate liver mitoses, they may act against cancer by increasing natural resistance factors.

Arsenic Content of Cigarette Smoke . . .

Holland et al. (U. of Texas) reported that the arsenic content of American cigarettes has increased from two to six times in the last twenty-five years. One cigarette contains 41 to 52.5 micrograms of arsenic. One third remains in the butt, one third in the ashes and one third goes into the smoke. About 5 micrograms of arsenic trioxide is inhaled from each cigarette. Three parts of arsenic trioxide per million is the maximum amount permitted in food by the Food and Drug Administration. Cigarette filters remove only about one third of the arsenic in the smoke. Arsenic in these minute doses attached to irritant tars might produce the metabolic and pathologic changes that result in lung cancer.

Oral Examination . . .

The Veterans Administration reports that inclusion of an oral dental examination in the physical evaluation given patients on hospital admission is proving valuable for early diagnosis of cancer. Since the technique was adopted generally by VA hospitals about two and a half years ago, the hospitals have reported some 700 cases of cancers of the mouth, tongue, and throat that might otherwise have been unidentified until too late for successful treatment. The oral examinations by dentists also are proving to be a contributing factor in improvement of overall diagnosis and treatment planning for patients in VA hospitals, especially for older patients.

LUNG CANCER

Certain Accomplishments and Needs in Lung Cancer Research

Dean F. Davies, M.D., Ph.D.

(Excerpted from paper presented in a Symposium on "Smoke, Smoking and Chest Diseases," May 27, 1959, at the 54th Annual Meeting of the American Trudeau Society, Palmer House, Chicago, Illinois.)

Mr. Chairman, Members of the American Trudeau Society, and friends:

During the past several years, busy physicians have found themselves at a disadvantage by the appearance in the public press of stories about smoking and lung cancer before publication of the original data in scientific journals. Even so, few physicians can afford to wade through the mass of scientific literature concerned with the environmental agents incriminated in lung cancer.

For purposes of convenience one's belief about the relationship between the factors implicated as causes (such as cigarette smoking or atmospheric pollution) and their effects (such as lung cancer) relates to evidence obtained at one of *five decision levels.*

Each level is characterized by a certain class of observers. The first level is that of *intuition.* In the 1920's and '30's many laymen spoke of cigarettes as "coffin nails." The evidence for this nickname was meager, if existent at all.

The second decision level is that of *clinical judgment.* It should not be deprecated too vigorously by the statisticians. It is clinical judgment that feeds medical science with hypotheses and supportive evidence. In the 1940's a few clinicians, by reason of their large experience with lung cancer, felt certain that one of its important causes was cigarette smoking.

The third decision level is that of *epidemiology.* During the early 1950's, many became convinced of the cause and effect relationship between cigarette smoking and lung cancer because of the statistically demonstrated correlation between the two. This decision level uses scientific evidence. However, the distinction between causal relationships and simple correlation of two events should be appreciated. The statement has been made repeatedly that the cause and effect relationship between cigarette smoking and lung cancer has been established on epidemiologic grounds. *Punctuating* statements of this type have been those from a *different* source, saying that statistics do not prove anything. In diplomatic circles this to and fro type of argument is called the "dialogue of the deaf."

The fourth decision level is that of *pathogenesis.* Over two years ago the Study Group on Smoking and Health concluded that ". . . every morphologic stage of carcinogenesis as it is understood at present, has been observed and related to the smoking habit." The Study Group, in this country, and subsequently the Medical Research Council of Great Britain; that of Sweden; the official advisory health organization of the Netherlands; the Surgeon General of the Public Health Service; and a special committee of the International Union against Cancer have all, in one way or another and independently, incriminated smoking as a causative factor in lung cancer. Their conclusions have been based on authoritative epidemiologic and pathogenetic evidence. Although the series of events — exposure to smoke by inhalation, localization of tar, penetration of epithelial cells, proliferative and neoplastic reaction of the epithelium — leave little doubt, certain gaps in the picture of pulmonary carcinogenesis remain. For example, an invasive epidermoid carcinoma of the lung, produced experimentally by tobacco smoke or natural atmospheric pollutants, has still not been reported in the literature.

Nevertheless, on the strength of the evidence we do have, most of those persons familiar with the literature consider it to be satisfactorily established that cigarette

smoking causes lung cancer. Yet they concede the probability that the same lines of reasoning and mechanisms may operate in exposure to atmospheric pollutants. The quantitative relationships between these two sources of inhaled particulates have not been adequately explored. Epidemiologic data are inadequate to fix a precise figure on the relative importance of the roles played by cigarette smoke and atmospheric pollution in the country at large. On the basis of existing data estimates of lung cancer cases associated with smoking have ranged between 50 and 90 per cent. Three quarters now seems to be a reasonable estimate. It is possible that pollution from the air is a necessary ingredient in some or all of such cases, but evidence on this is quite tenuous.

The fifth decision level is that of "*proof positive*". It is characterized by purists as well as by those who, for reasons of their own, would prefer to rationalize as long as possible. With a human population, the closest thing to proof of a causal relationship between inhalants and chest diseases would be a withdrawal study.

The evidence is highly suggestive that such a withdrawal study would be succesful for lung cancer at least, assuming that a randomly selected population of smokers could be persuaded to stop smoking.

The hypothesis that cigarette smoking is causally related to coronary thrombosis and to noncancerous chest and other diseases associated with smoking could be attacked simultaneously by such a study on the effect of withdrawal.

Further research activities needed on lung cancer include:

1. Studies of host factors such as those of genetic, immunologic and psychologic origin and the effect of previous disease in determining susceptibility and resistance.
2. Further studies on pathogenesis.
3. Good epidemiologic studies on air pollution.
4. Studies on habituation to smoking and its psychologic and pharmacologic cause.
5. Research aimed at reducing the cancer-producing effects of cigarette smoking.

The American Cancer Society, in addition to its large-scale epidemiologic study, has had a separate Advisory Committee specifically concerned with research on lung cancer. This committee has been concentrating on these problems for many years and is supporting and exploring research possibilities in each area.

Tumor of the Jaw—Benign or Malignant?

Most tumours of the jaws are innocent cysts, which radiologically appear translucent and unilocular with well-defined margins, and show no bone erosion or adjacent periosteal reaction. A tooth, or a portion of one, is usually distinguishable in radiographs of dentigerous cysts. Malignant tumours, on the other hand, generally cause bone destruction, revealed radiologically as areas of translucency of varying size, with occasionally some sub-periosteal new bone formation. The "soap-bubble" and "sunray" appearances have been mentioned.

Ellis, M.: Malignant tumours of the jaw. In Raven, R. W., Ed.: Cancer, Vol. 4. London. Butterworth & Co., Ltd. 1958; p. 33.

Pincus and coadjutors (Worcester Foundation) have found that the animal body can synthesize cholesterol from squalene and zymosterol, a substance similar to ergosterol of yeast and other plants. They suggest that either a tumor may stimulate the body to produce cholesterol or the body may produce cholesterol in response to stress of the tumor. Under stress of any kind the adrenals enlarge and their cholesterol content increases. Necrotic portions of tumors contain great quantities of cholesterol, but it is not known whether the tumor manufactures or merely traps it.

Ackerman (Washington U.) recently reviewed progress in cancer control. Today about two thirds of all cancer cases are not being cured. Included in this group are 75,000 who die needlessly. They could have been cured through early detection and prompt treatment. Even where cancer cannot be cured it may become a chronic disease permitting many years of useful and tolerably comfortable life. A patient with incurable cancer may live even 20 years. Cancer of the lung might be prevented if heavy smoking were curtailed.

Scott (Washington U.) in a recent talk said that from a study of leukemia with its readily available blood and tissue cells we may learn much concerning neoplastic diseases. It is probable that the cause of cancer will be found from research in leukemia. For this reason the American Cancer Society is supporting forty research grants directed toward the cause, course and cure of leukemia, and twenty-six grants for basic research related indirectly to the cause of leukemia. Over a million and a half dollars are invested in these grants, making ACS the leading voluntary health organization in research on leukemia.

Pierce (U. of Chicago) recently reviewed the problem of leukemia and suggested the directions that further research should take. (1) Epidemiologic inquiry into predisposing factors -- exposure to radiation, socioeconomic environmental factors and mental health. (2) Search for a test for leukemic cells before they can be detected in the peripheral blood or bone marrow. (3) Study of differences between normal and leukemic cells -- by electron microscope, by histochemical methods for exploring the enzyme systems and nucleic acid metabolism. (4) Study of the effect of viruses on leukemias in fowls and rodents. (5) Search for more effective chemotherapeutic agents.

Kaplan (San Francisco): Experimental evidence in-

dicates conclusively the existence of indirect mechanisms (disturbances in normal tissue regulatory mechanisms) of carcinogenesis. The agents do not appear to act directly upon the cells which become neoplastically transformed.

Colter, Kritchevsky and Koprowski (Wistar Institute): RNA is infective. Infection has been obtained with RNA from 1) Ehrlich ascites tumor cells bearing Mengo and West Nile encephalitis virus; 2) polio-infected hamster brain and spinal cord; and 3) cells bearing the tumor-inducing viruses of Gross and Stewart...Rabbit antisera against the nucleoproteins (RNP and DNP) of mouse ascites tumors have inhibited the growth of these tumors. Perhaps even more important, antiserum against one tumor type inhibits the growth of several others -- an indication that the cancers have an immunological common denominator. When these tumors are incubated in vitro with glycine-C^{14} and antiserum, label incorporation into cell protein and nucleic acid is inhibited, and 50 per cent of the cell protein and RNA is lost during 90 minutes of incubation. Antisera against MCN strain tumor cells inhibit fibroblast-like cells only; antisera against HEP and HeLa cells inhibit epithelial type cells. Anti-RNP and anti-DNP antisera have different mechanisms of action.

Sanford (NCI): A single cell was isolated from normal mouse tissue and cultured. It divided into 1) a daughter cell whose cultured offspring almost always gave rise to tumors when transplanted to mice and 2) a daughter giving rise to a strain which never produces mouse cancers.

Weinhouse (Institute for Cancer Research, Philadelphia): Cancer cells subsist on sugars and fats as normal cells do, and they burn them in the same proportions. Cancer's voracious appetite may be due to the fact that its cell membrane is highly permeable to sugar. If this proves to be the case, it may be possible to exploit that appetite with toxic analogues specific for cancer cells.

Sommers (Boston University): Pituitary cell counts at autopsy show imbalances involving the function of thyroid, adrenals and ovaries in most cancers of the breast, endometrium, lung, prostate and, to a lesser degree, stomach.

Fishman (Tufts): Blood levels of acid phosphatase have been found elevated in more than 80 per cent of prostatic cancer cases investigated, while beta glucuronidase levels were high in 80 per cent of cervical cancers.

COMING MEDICAL MEETINGS

Date 1959	Meeting	City
Aug. 10-13	National Medical Association	Detroit
Aug. 12	Pan-American Congress of Otorhinolaryngology and Bronchoesophagology	Rio de Janeiro
Aug. 17-22	International Congress for Speech and Voice Therapy	London
Aug. 20-22	Rocky Mountain Radiological Society	Denver
Aug. 20-27	International Congress of Genetics	Montreal
Aug. 24-27	American Hospital Association	New York City
Aug. 30- Sept. 6	International Congress for the History of Science	Barcelona and Madrid
Aug. 31-Sept. 4	World Conference on Medical Education	Chicago
Sept. 6-12	College of American Pathologists	Chicago
Sept. 7-11	American Society of Clinical Pathologists	Chicago
Sept. 7-12	European Society of Haematology	London
Sept. 7-12	World Medical Association	Montreal
Sept. 9-10	International Congress on Air Pollution	New York City
Sept. 9-12	Electron Microscope Society of America	Columbus, O.
Sept. 10-12	American Association of Obstetricians and Gynecologists	Hot Springs
Sept. 12-13	International Symposium on Anti-Infectious and Antimitotic Chemotherapy	Geneva
Sept. 12-19	Federation Dentaire Internationale	New York City
Sept. 13-15	Medical Progress Assembly	Birmingham
Sept. 13-17	International College of Surgeons, North American Federation	Chicago
Sept. 13-17	International College of Surgeons, United States Section	Chicago
Sept. 14-18	American Dental Association	New York City
Sept. 18-20	International Cardiovascular Society	Munich
Sept. 19-26	American College of Gastroenterology	Los Angeles
Sept. 21-24	International Union of the Medical Press	Cologne
Sept. 21-Oct. 3	International Congress of Cancer Cytology	Madrid
Sept. 22-25	American Roentgen Ray Society	Cincinnati
Sept. 24-26	American Association of Medical Clinics	Chicago
Sept. 24-26	Central Association of Obstetricians and Gynecologists	Chicago
Sept. 28-Oct. 2	American College of Surgeons	Atlantic City
Oct. 2-3	American Medical Writers' Association	St. Louis
Oct. 4-7	Texas Academy of General Practice	Galveston, Texas
Oct. 5-7	Association of Medical Illustrators	Seattle
Oct. 5-8	American Academy of Pediatrics	Chicago
Oct. 5-9	American Society of Anesthesiologists, Inc.	Bal Harbour, Fla.
Oct. 11-16	American Academy of Ophthalmology and Otolaryngology	Chicago
Oct. 23-25	American College of Cardiology	Philadelphia
Nov. 7	Penrose Annual Cancer Seminar	Colorado Springs

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